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MODERN METHODS IN THE DIAGNOSIS AND TREATMENT OF RENAL DISEASE

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MODERN METHODS IN THE DIAGNOSIS AND TREATMENT OF RENAL DISEASE

BY

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PREFACE

THIS monograph was written in response to requests from various medical men who felt the need of a short practical account of some of the newer methods employed in investigating the renal function. In recent years considerable advances have been made in this branch of medicine, but much of the work lies scattered throughout the literature of various countries and is not accessible to the busy general practitioner. The present volume is an attempt to satisfy this want; it comprises, to a certain extent, work that has already been published by the author, chiefly in conjunction with Dr. O. L. V. de Wesselow, of St. Thomas's Hospital.

Since the book is intended principally for the general practitioner, it contains only the briefest allusions to theoretical points, and no references to literature are given. The statements made in connection with the various tests are founded on a very extensive experience of renal patients, and only those tests have been included which were found to be of practical clinical value and which are easily carried out.

In connection with the subject of renal tests a word of warning may perhaps be necessary. In every case the clinical symptoms must be carefully considered, but, as this part of the subject is discussed in all the ordinary text-books, it was considered superfluous to devote much space to it here. The necessity for a thorough study of the clinical manifestations cannot, however, be too strongly emphasised. In many patients, especially in

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the earlier stages of disease, a careful correlation of the clinical condition with the results of the tests described will give information which could not possibly be obtained, in the present state of our knowledge, from a study of the clinical features alone.

H. MACLEAN.

LONDON,
October, 1921.

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MODERN METHODS IN THE DIAGNOSIS AND TREATMENT OF RENAL DISEASE

CHAPTER I

THE CHIEF FUNCTIONS OF THE KIDNEY

In spite of the many ingenious and laborious investigations that have been carried out in an endeavour to elucidate the manner in which the kidney performs its functions, many of the problems of renal secretion are still unsolved. The chief functions performed by the kidney we know; how the kidney performs them remains a comparative mystery. The extreme complexity of this gland, with its various tubules and cells, has always attracted and baffled physiologists and histologists, so that to-day we are in some respects less certain of the methods of renal secretion than we seemed to be some years ago.

One of the principal functions of the normal kidney is the excretion of water. In addition to this, it performs certain other very important duties, the chief of which may be summarised as follows:—

(1) Removal from the body of certain waste products of nitrogenous metabolism.

(2) Removal of acid products from the body.

(3) Maintenance of the optimum concentration of salts in the fluids and tissues.

(4) Excretion of many toxic materials artificially introduced.

From the point of view of investigating the efficiency of the kidney we are chiefly concerned with the first three functions, and, in order to appreciate certain of the facts

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described later on, it is necessary to discuss these functions somewhat more fully.

(1) Excretion of Waste Products of Nitrogenous Metabolism and Urine Secretion Theories.

The chief nitrogenous products of protein metabolism in the body are urea, uric acid, creatinin, and purin bodies. These substances are present in the blood in comparatively small amount. They are brought to the kidney in solution in the blood plasma, and are excreted in the urine by the kidney cells. The kidney, however, has the power of concentrating these bodies to a very great extent, so that a given volume of urine may contain 60 to 100 times the amount of these products present in an equal volume of blood. The following table gives a rough idea of the percentages of these substances present in human blood and urine respectively and the concentration brought about by the kidney. The figures were obtained from an experiment on a healthy young adult.

Table 1.

	Concentration in blood per 100 c.c.	Concentration in urine per 100 c.c.	Number of times substance concentrated by the kidneys.
Urea . .	25 mgrs.	1,800 mgrs.	72
Uric acid .	2 ,,	58 ,,	29
Creatinin .	2·2 ,,	89 ,,	40

This power of concentration on the part of the kidney may be even greater than is indicated by the above figures, especially in the case of urea. When the renal cells are diseased, the power to concentrate becomes markedly reduced, and some general idea of the extent to which the kidney is damaged may be ascertained by an estimation of the concentrating power for any of the

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substances mentioned. In practice it is usually found most convenient to deal with the concentrating power for urea, since this substance is easily estimated, both in blood and urine. Details of the method of procedure are given later (pp. 44 and 54).

Theories of Renal Secretion.

Various theories have been advanced from time to time to explain the mechanism of renal excretion. The latest attempt to gather together the available information and to create order out of chaos was made by Cushny in his excellent monograph on "The Secretion of the Urine." Cushny discusses very fully all the well-known theories, but is unable to accept any one of them in its entirety. He propounds a solution which retains certain of the ideas of former investigators, but is in its principal bearings essentially his own. Cushny takes the view that the first act in kidney secretion is the filtration of the liquid part of the blood through the glomeruli into the renal tubules. The filtrate contains in solution all the soluble bodies which are normally present in the blood, so that the glomeruli merely seem to separate the blood corpuscles and colloidal protein from the liquid part. At this stage the parts of the tubules immediately connected with the glomeruli contain a liquid which has practically the same concentration of soluble bodies as the plasma of the blood. As this liquid passes down the tubules water is reabsorbed, so that the solution becomes more and more concentrated. If water alone were reabsorbed, however, each substance would be concentrated exactly the same number of times, but experiment shows that this is not so, for, in any given individual, urea may be concentrated 80 or 90 times, while the uric acid in the urine may not be more than 20 or 25 times that in the blood. To explain this it is necessary to assume that uric acid is partly reabsorbed with the water, and the general idea advanced is that any substance which may be of further use in the body is, to a greater or less extent, reabsorbed with the water, while such a definite

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end product as urea, which is of no further use in the body, is all excreted. Various other anomalies with regard to the excretion of such substances as salt and sugar in normal urine are explained on a similar hypothesis. The theory is an attractive one, and most helpful in a general way in that it presents a concise conception of renal action. To its author we owe a debt of gratitude for his critical presentation of the known facts of kidney activity; but, unfortunately, when we apply the theory to certain pathological conditions, it fails to account for the facts. In short, while the author seems to have proved that water is reabsorbed from the renal tubules, there is no real evidence that soluble substances, such as uric acid, sugar, etc., are at all reabsorbed. In fact, it is very doubtful whether the original process in excretion is an ordinary filtration at all. Many facts are more in accordance with the view that the glomerular epithelium possesses a selective action, and that, while the passage of water may be a filtration, the glomerular cells possess the power of concentrating to different degrees the various substances brought to them in the blood. It is reasonable to suppose that the glomerular epithelium will not allow certain bodies, such as sugar, chlorides and uric acid, to pass into the tubules until their concentration in the blood reaches a certain grade. To such substances the name of "threshold bodies" has been applied. In the case of other products, such as urea, ammonium, creatinin and foreign substances — "the non-threshold bodies" — elimination takes place whenever they are present in blood quite irrespective of concentration. Now, if it be allowed that urea and creatinin are non-threshold bodies, they must be each concentrated in the urine the same number of times, the total amount present in the urine depending on the amount in the blood. Various experiments carried out by the writer definitely prove that this is not so. For instance, in one case of severe subacute nephritis the blood plasma contained 600 mgrs. urea per 100 c.c., while the amount of creatinin was 5 mgrs. per 100 c.c.

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The sample of urine collected during the hour the blood was drawn contained 1,200 mgrs. urea and 60 mgrs. creatinin per 100 c.c. In this case the urea was concentrated only twice, while the creatinin was concentrated twelve times. The theory, however, requires that the creatinin in the urine should be concentrated only twice, like the urea. Similar anomalous results can be obtained in normal subjects. Various other experiments could be quoted which necessitate a revision of Cushny's theory. For instance, in a case of diabetes the patient's blood plasma contained 0·24 per cent. sugar and the urine 1·2 per cent. Now, if the threshold value of sugar be taken as the highest concentration in the blood below which sugar is not excreted, experiment shows that the value is about 0·17 per cent. In this particular patient it appeared to be almost exactly 0·17 per cent. Whenever blood sugar rises above the region of 0·17 per cent. the normal kidney begins to excrete sugar. According to theory, fluid containing 0·24 per cent. of sugar should filter through the glomerular epithelium into the tubules, where there should be a reabsorption of a fluid containing 0·17 per cent. of sugar, leaving 0·07 grm. of sugar in the tubule for each 100 c.c. of fluid absorbed. Now, an estimation of the blood and urine urea showed that urea in this patient was concentrated 54 times. In other words, 5,400 c.c. plasma fluid passed through the glomeruli for each 100 c.c. of urine formed, 5,300 c.c. fluid being reabsorbed. The total amount of sugar present in 5,400 c.c. plasma fluid was 0·24 grm. $\times$ 54 = 12·96 grm. If the reabsorbed fluid contained 0·17 per cent. sugar, then it follows that 53 $\times$ 0·17 grm. = 9·01 grm. sugar must have been reabsorbed. The difference between this amount and the total quantity present (12·96 — 9·01), = 3·95 grm., should be present in the 100 c.c. urine. The actual amount found in the urine was only 1·2 per cent. Since, however, the blood of a healthy individual contains about 0·1 per cent. sugar, and practically no sugar appears in normal urine, it might be argued that only 0·1 per cent.

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sugar would be reabsorbed in the tubules. In a normal person, for obvious reasons, there must be an absorption of at least 0·1 per cent. sugar according to the theory, since normal urine is free from sugar, and the tubular filtrate must have contained 0·1 per cent. sugar. If, therefore, we assume that in the diabetic case described the absorption from the tubules was 0·1 per cent. sugar, the total amount absorbed would be 5·3 grm., leaving 7·66 grm. in the 100 c.c. urine ; as stated above, the actual figure found was 1·2 per cent.

Various other experiments gave similar results, so that, on the whole, while the theory is useful, it can hardly be accepted *in toto* as an explanation of the mechanism of urine secretion. All the various other theories are even more unsatisfactory in some respects, so that at present nothing definite can be said on this point.

(2) Removal of Acid Products from the Body.

In the process of metabolism, acids are produced which are exceedingly toxic if allowed to accumulate in the body. One very important part played by the kidneys is the elimination of acid, for when this function fails serious changes result. The blood plasma is maintained at a practically constant reaction, being very slightly more alkaline than distilled water. Normal urine, on the other hand, is distinctly acid when tested in the usual way by indicators. In modern nomenclature, the H–ion concentration of the urine is considerably greater than that of the blood, and this change is brought about by the kidney. The elimination of acids on the part of the kidney is a very extensive process, for it has been calculated that acid corresponding in amount to from 3 to 3·5 grm. of pure sulphuric acid may be removed from the normal body per day. Generally, whenever acid is to be eliminated from the body it combines with any base available and is brought to the kidney in the form of a salt. The acid-eliminating function of the kidney resolves itself into an attempt to get rid of the acid part of the molecule while retaining as

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much as possible of the base with which the acid radicle is combined. It cannot, however, separate a strong acid from a base and eliminate the acid. In the case of a body like sodium sulphate, for instance, it cannot divide the substance into an acidic and a basic part and eliminate the acid. What the kidney really does is to change the practically neutral mixture of phosphates in the blood to the acid mixture which we find in the urine. In the blood we have a balanced mixture of phosphates consisting of the monosodium phosphate (NaH_2PO_4), which acts as a weak acid, and the disodium phosphate (Na_2HPO_4), which acts as a weak base. As long as the relative proportion of these two salts in a solution remains constant no change in reaction takes place. An increase of the disodium phosphate would tend to shift the reaction to the alkaline side, while any increase in the monosodium phosphate would shift it to the acid side. Now, for all practical purposes the reaction of the urine depends on the mono- and di-sodium phosphates present, and the acidity is due to the fact that the mixture of phosphates is composed of a larger amount of acid phosphate relatively to the amount of basic phosphate. The kidney therefore deals with a mixture of acid and basic phosphates in definite proportions and secretes a fluid in which the proportion of acid to basic phosphate is considerably increased. This it does of course at the expense of the basic phosphate (Na_2HPO_4) of the blood. This basic phosphate is changed in the kidney into acid phosphate (NaH_2PO_4), so that an atom of phosphorus which formerly was combined with two atoms of sodium as Na_2HPO_4 is now excreted in combination with only one atom of sodium as NaH_2PO_4. Thus for each molecule of acid phosphate eliminated one atom of sodium is saved and retained in the blood. This reaction may be expressed as follows :—

$$Na_2HPO_4 + H_2O = \underset{\text{Retained by body as carbonate.}}{NaOH} + \underset{\text{Excreted.}}{NaH_2PO_4}.$$

This is the chief mechanism involved in eliminating acid,

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and in patients in whom this function is defective there is an accumulation of phosphates in the blood, accompanied very often by definite toxic symptoms. Indeed, there is some evidence that failure to eliminate acid is of more importance in producing definite clinical symptoms than is failure to eliminate the nitrogenous waste products of metabolism. Both defects are commonly found together in the same patient.

Acidosis in Renal Disease.

Obviously, the elimination of acid from the body tends to preserve the normal reaction of the blood, so that in patients in whom the mechanism is defective a condition is produced which is often referred to as acidosis. In order to follow what is meant by this term it is necessary to consider very briefly the mechanism by which the normal blood reaction is maintained constant. It is a noteworthy fact that the blood reaction, even under the most adverse circumstances, never changes to any appreciable extent. All that happens is that in certain diseased conditions it may tend to shift its H-ion concentration slightly towards the acid side, but even this rarely happens to any appreciable extent, except perhaps in moribund patients. For practical purposes we may, therefore, state that during life the blood reaction remains constant under all conditions, and that such a change as the blood becoming acid, a condition which is sometimes described in medical literature, is a figment of the imagination. The means by which a constant blood reaction is maintained is somewhat complex, but the general mechanism is essentially dependent on the principle of balanced solutions, as already described for the phosphates. In the blood, however, the chief system utilised for this purpose is not a phosphate one, but a system consisting of H_2CO_3 and $NaHCO_3$, the reaction of the mixture depending on the relative amounts of the two substances present. The absolute amounts present do not matter. When the amount of carbonic acid increases the solution becomes more acid, while any

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increase in the sodium bicarbonate renders it more alkaline. Various other substances, such as phosphates, proteins, and hæmoglobin, play a part in maintaining the normal blood reaction, but it is unnecessary to consider them here.

For efficiency this system, $\frac{H_2CO_3}{NaHCO_3}$, requires that any change produced in one factor may be compensated for in the other, in order to maintain the normal ratio. A comparatively large decrease in the amount of H_2CO_3 present, for instance, will not change the blood reaction, provided that there is a corresponding decrease in the $NaHCO_3$. Now, various mechanisms combine in the body to maintain this normal relationship, and one important mechanism is the kidney. For instance, if the CO_2 in the blood is somewhat depleted, as happens when a person is subjected to a rarefied atmosphere, we have, potentially at any rate, a relative increase in the sodium bicarbonate, and so a tendency to increased alkalinity—in fact, an alkalosis. This is prevented by the kidney throwing out the excess of $NaHCO_3$, so that the relative proportions of H_2CO_3 and $NaHCO_3$ are preserved. When the kidney is deficient in the elimination of acid an abnormal amount of acid is retained in the body, with the result that some of it combines with the sodium of the $NaHCO_3$ and so lowers the basic factor in the system. In such a case a corresponding decrease in the H_2CO_3 is brought about by increased ventilation, consequent on increased action of the respiratory centre. In diseases in which large amounts of organic acids are formed in the body (as, for instance, in diabetes) there is the same tendency for a lowering of the bicarbonate of the blood. Both in severe nephritis and in diabetes, therefore, there is a decrease in the sodium bicarbonate of the blood; and since Van Slyke suggested that a condition in which the blood sodium bicarbonate was lowered constituted acidosis, we see that in this sense of the term acidosis may be present in renal disease. This definition of acidosis is not necessarily a good one, and

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much of the chaos with which the designation "acidosis" is at present surrounded depends on the fact that authorities are not agreed as to what they mean by the term. The most common-sense view of acidosis would be a condition in which excessive amounts of acids were present in the system. Such a condition is diabetes. In this disease large amounts of organic acids are passed in the urine, largely in combination with ammonia, so that this acidosis is accompanied by a considerable increase of the so-called "free ammonia" (ammonia combined with acid as an ammonium salt) in the urine. Naturally, there is also a diminution of the blood sodium bicarbonate, just as in nephritis, so that diabetic acidosis also fulfils Van Slyke's definition. In nephritis, however, there is no acidosis in the sense of increased "free ammonia" or "acetone bodies" in the urine. The so-called acidosis is merely represented by a diminished sodium bicarbonate content in the blood. Why some of the retained acid does not combine with ammonia and, on excretion as an ammonium salt, increase the "free ammonia" of the urine is unknown.

In any case of acidosis there must be a retention or increase of acid in the body, giving rise to a lowering of the sodium bicarbonate value. It does not follow, however, that every case in which the sodium bicarbonate is below normal constitutes an acidosis. Indeed, as already indicated, it can be easily shown that such a condition may result from an initial alkalosis. Of the various tests for acidosis, one of the simplest is that suggested by Sellard, who gives by mouth definite amounts of sodium bicarbonate. When acidosis is present the alkali is retained to neutralise the acids present, so that large amounts may be taken before any appears in the urine. A normal subject will pass an alkaline urine after taking 5 to 10 grm. of sodium bicarbonate, while a patient with acidosis may require over 100 grm. In severe nephritis it was often found that patients could take large amounts of alkali without passing an alkaline urine, and this was taken as evidence of acidosis.

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The fact is that in such patients the defective kidney fails to eliminate the alkali, and its retention does not necessarily indicate acidosis at all. Sellard's test is of no value as an indication of acidosis in nephritis.

(3) The Maintenance of Optimum Concentration of Salt in the Body Fluids.

The principal salt in the body is sodium chloride, and though small amounts of other chlorides are present, it is customary to express the total chlorides in terms of sodium chloride. The body cells require a fluid containing about 0·6 per cent. sodium chloride, and any marked change in this value is incompatible with life. When salt is taken with food in the usual way, there is a slight increase of this substance in the blood, and the kidney immediately throws out the excess. When, for any reason, the amount of salt tends to get below 0·6 per cent., the necessary concentration in the blood is maintained by the kidney throwing out water. Thus, under normal conditions, the kidney acts as a most efficient mechanism, preserving the optimum concentration of salt in the body fluids. In renal disease, the salt-excreting function of the kidney may be considerably reduced or even lost, and various methods have from time to time been suggested to test this function. It is, perhaps, not generally understood that the retention of sodium chloride in the system, of necessity involves the retention of water as well, so that the condition is very soon indicated by œdema. It is therefore never necessary to perform a test for salt tolerance, for it may be taken for granted that if no œdema is present, salt is excreted quite well. If salt is retained, it must be present in the body in a concentration of about 0·6 grm. per 100 c.c. fluid, so that for each 0·6 grm. of salt retained the body will retain about 100 c.c. of water. If, on the other hand, the difficulty is to excrete water, then an equivalent amount of salt will be retained to give the optimum salt concentration. It is difficult, if not impossible, in any given case in which salt is not excreted in the urine, to say whether the primary

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defect is inability to excrete salt or inability to excrete water. Either condition produces the same result—œdema and ascites. Whatever the cause of the œdema, it always results in the retention of the optimum amount of salt. This is well seen in pneumonia, where the large exudation in the lung retains sufficient salt to give the usual salt concentration of about 0·6 per cent. Tests for sodium chloride excretion are therefore superfluous, but even if they were not so, it is quite useless to give a large dose of sodium chloride by mouth and ascertain how much of this is excreted in a given time, for the result will depend quite as much on other factors as on the condition of the kidney. French observers and others have shown that the ingestion of a large amount of salt does not necessarily mean that an equivalent amount should be excreted by a healthy individual. The amount of salt excreted after a given dose depends on the state of the tissues with regard to fluid. The amount of fluid present in the body varies considerably at different times, the actual amount, perhaps, depending to some extent on the quantity of sodium chloride available. If the body happens to be low in fluid, the ingested salt is retained in order that the fluid may be increased on the principle already described. According to circumstances, salt given to a healthy subject may be eliminated to a great extent, or retained in order to increase the total amount of body fluid.

To ascertain whether or not a patient excretes salt normally, it is necessary to get salt equilibrium established by careful dieting and to follow this with large doses of salt repeated for several days. If the salt is retained, an increase in weight takes place both in the healthy and diseased individual owing to the increase in fluid, but since this increase, when it takes place in the healthy subject, is limited to a few days, the latter excretes in his urine after three or four days an equivalent amount of salt to that taken by mouth. On the other hand, the nephritic whose salt elimination is deficient does not respond in this way, but accumulates more and more

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fluid until, if the ingestion is prolonged, marked œdema and ascites supervene. It is difficult to investigate salt retention on the above lines, and for practical purposes such tests are quite unnecessary. It is important to note that retention of sodium chloride, unlike retention of urea or other nitrogenous substances, never increases the concentration in the blood. Even in cases of nephritis in which no sodium chloride at all is passed in the urine, the concentration in the blood remains the same as in the normal individual. These observations are of practical importance, for it is by no means an uncommon occurrence for nephritic patients to be limited to salt-free diets in cases where no œdema results. Such treatment imposes a good deal of discomfort on the patient and is inconsistent with physiological facts. The retention of water in patients who are able to excrete little or no sodium chloride is so very definite that the increase of weight of the patient may be fairly accurately gauged from a knowledge of the salt retained. The results of failure or defect in the various renal functions as seen in renal disease may now be discussed.

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CHAPTER II

THE KIDNEY IN DISEASE

Like many other organs, the kidney is liable to be affected by acute and chronic diseases. From the point of view of the clinician, perhaps the most interesting symptoms are those seen in severe acute nephritis. Here, as well expressed by Auld, the kidney tissue may be compared with a pneumonic lung, and the whole of the kidney functions are for the time being thrown more or less out of action. In consequence there is a failure to eliminate nitrogenous waste products, with the result that these bodies accumulate in the blood. Little or no sodium chloride is present in the urine, and water which should be eliminated is retained in the body, giving rise to œdema and dropsy. The acid-eliminating function of the kidney fails to fulfil its purpose, and the retained acid products tend to upset the normal mechanism for the regulation of the blood reaction. This condition generally persists for some time, but sooner or later, in favourable cases, the renal cells recover their function to some extent, and marked general improvement sets in. All the features of renal deficiency are most marked in acute disease, but the same manifestations, though in a modified degree, are present in chronic disease, and as far as the kidney is concerned many of the symptoms of acute nephritis differ only in degree from those of chronic nephritis.

Acute Nephritis.

Acute nephritis is the result of some infection, which may be severe or so trivial that its presence cannot be ascertained. Many cases of the disease are associated with a sore throat; sometimes it is accompanied by extensive

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broncho-pneumonic changes in the lungs. Occasionally a possible source of infection may be found in an external wound. The incidence of acute nephritis was very much increased during the Great War, when an epidemic of so-called "war nephritis" constituted a serious medical problem. The exact causation of this war nephritis has never been definitely settled, but a good deal of evidence pointed to the conclusion that it was an insect-borne disease—probably a louse infection. This nephritis presented the usual symptoms of nephritis as seen in civil life, but, unlike these latter cases, it was characterised by the presence of an important symptom—marked dyspnœa. Various observers attempted to ascribe to the disease certain features which were said to be uncommon or even absent in civilian practice, thus inferring that the malady was a new variety, with new manifestations. Further study, however, has demonstrated that many cases seen in civil life often show exactly the same symptoms as have been described in war nephritis. It must be allowed that the marked dyspnœa of war nephritis, already referred to, is less common in civilian cases, but even this symptom is perhaps not so rare as we were led to suppose. Possibly the strenuous conditions of life under which the disease manifested itself at the front played no little part in the production of the dyspnœa. At any rate, there is no essential difference between acute "war nephritis" and acute nephritis as seen in civil practice.

General Symptoms of Acute Nephritis.

A full account of the chief manifestations present is to be found in any text-book, so that only a brief reference to the outstanding clinical features is necessary here.

The chief symptoms of the disease are :—

(1) General malaise.
(2) Œdema.
(3) Headache.
(4) Dyspnœa (marked in war nephritis).
(5) Vomiting.

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(6) Pain.
(7) Fever.
(8) Changes in the urine and in the blood.
(9) Vascular changes.
(10) Eye changes.

The extent to which these symptoms are present depends on the severity of the attack. Often, in mild cases the condition is revealed by an examination of the urine, the patient simply feeling somewhat "out of sorts," without any other prominent symptom. Perhaps the most important feature is the presence of œdema, and the other symptoms described may be present in whole or in part according to circumstances.

Œdema is present to some extent in practically every case. In severe cases it is general in distribution and often extreme, while in milder cases it may be limited to puffiness of the face on rising in the morning or slight œdema of the feet and ankles in the evening. With improvement it usually disappears last from the area over the sacrum and from the ankles. It may be accompanied by effusions into the serous sacs.

Headache is very commonly complained of, though sometimes it may be absent. Often, it is most marked in cases accompanied by severe œdema, and disappears with the subsidence of the œdema.

Dyspnœa was always present in "war nephritis," and was frequently the first symptom complained of. It manifested itself either as a continuous dyspnœa due to pulmonary complications associated with cyanosis, or as paroxysmal dyspnœa without cyanosis. Though not so frequent in civil practice, the writer has seen patients in whom this symptom was quite marked. Cough is occasionally present.

Vomiting may be present at the outset of the disease, or, in the absence of vomiting, nausea may be present.

Pain in the lumbar region may be an early symptom, and frequency of micturition with "scalding" is occasionally met with.

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Fever is sometimes present, but is certainly not an essential feature of the disease. Large numbers of patients suffering from war nephritis, when examined in France at an early stage, were found to be afebrile.

Urine.—In the majority of cases oliguria is probably present early in the disease, though, as the result of improvement, this may soon be replaced by excessive secretion.

Occasionally complete suppression is noted, and in some cases the patient at first passes only a few ounces per day. With improvement a very marked and often abrupt rise in the secretion of urine is the rule, the amount falling with the disappearance of the œdema.

During the early stages the urine generally contains a large amount of protein, which in favourable cases decreases more or less rapidly, and may almost entirely disappear within a week or a fortnight. In other cases the albuminuria persists indefinitely, although the amount of protein is generally much less than was at first present. Blood is, perhaps, always present, though sometimes only in microscopic amount. Often the blood is obvious to the naked eye. As a rule the amount of blood bears no relation to the amount of protein. Casts are always present, and are usually mainly of the hyaline, epithelial and hyalo-granular varieties. Blood casts are also found in many cases.

During the early acute stage of the disease the urinary chlorides are often much reduced in amount and may be absent. Later on, the concentration may be greater than normal, due to the elimination of retained salt. The presence or absence of chlorides depends chiefly on the severity of the attack.

The Blood.—Except in the mildest cases, there is generally some accumulation of nitrogenous bodies in the blood, due to the inability of the kidney to perform its normal function. As already indicated, the chief of these bodies are urea, uric acid, creatinin and purin bodies, generally included under the term " non-protein nitrogen," and the

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extent of their concentration in the blood gives a most useful indication of the progress of the disease towards recovery or otherwise. Of these bodies urea is most easily estimated, and so its concentration is generally relied on for information in nephritic investigations.

So far the points mentioned are well recognised in acute nephritis. It is perhaps not so well understood that many of the features which were formerly supposed to be associated with chronic nephritis may be present at certain stages of the acute disease as well. Particularly interesting from this point of view is a study of the cardio-vascular, eye and blood changes, often associated with acute nephritis.

Blood Pressure in Acute Nephritis.

Special opportunities for the study of this feature were afforded in the epidemic of war nephritis already referred to. Just as in chronic nephritis the blood pressure is often raised, so it is found to be raised in many cases of acute nephritis. This increased blood pressure in the acute disease is almost invariably present when œdema is well marked, and it quickly returns to a normal or even an unusually low level with the subsidence of the œdema. Usually the rise is of moderate extent only, systolic readings above 180 mm. or diastolic readings above 110 mm. of mercury being rare. The blood pressure fall may occur by lysis or by crisis, and the critical falls are often very sharp and abrupt. Thus, in a case of this type a systolic pressure of 180 mm. and a diastolic pressure of 98 mm. dropped to 100 and 63 mm. respectively within 72 hours, while, in a case in which the pressure came down gradually, the systolic pressure fell from 152 to 100 mm. and the diastolic from 100 to 63 mm. in the course of 14 days. Between such extremes every variety of type of fall is seen, and in some instances the general downward course of the curve is broken by temporary rises.

Generally the diastolic pressure follows closely the curve of the systolic, but its variations are less marked; it rises

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and falls to a less extent than the systolic, and consequently the systolic-diastolic interval, which is greater than usual during the period of increased pressure, approximates more and more closely to the normal as the blood pressure falls. In a typical case this interval, which was represented by about 70 mm. of mercury during the period of raised tension, fell to about 40 mm. on the recovery of normal pressure. In the majority of patients the fall in blood pressure appears to be connected with a rise in the rapidity of the pulse. As a rule, the pulse rate is slow during the period of raised pressure, and in some cases may be as low as 40 per minute. When the fall of pressure is sudden, increase of pulse rate may be accompanied by tachycardia and palpitation. Occasionally, on the other hand, the pulse rate remains steady or even slows as the blood pressure falls.

It is important to note that during the period of raised tension there is frequently a marked difference in the height of morning and evening pressure, the latter always being the higher. In some instances this difference may amount to as much as 40 mm. of mercury. When the pressure returns to normal this excessive evening rise disappears.

Occasionally, the blood pressure may fall to a low level before the œdema has disappeared, but this appears to be rare, and in the great majority of cases there is a very close relationship between the termination of the period of raised blood pressure and the clearing up of the œdema. When the blood pressure persists for some time after complete disappearance of œdema, the possibility of accompanying chronic disease must not be overlooked. Relapses with reappearance of œdema are sometimes accompanied by a slight temporary rise in blood pressure.

Hydræmia or Excess of Fluid in the Blood.

In the majority of all cases with œdema, and in a few cases without œdema, there is an increase of the fluid part

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of the blood, so that the percentage of blood solids is less than normal. In other words, the blood is "watery." When drawn into a tube containing a little potassium oxalate to prevent coagulation and allowed to stand, the red corpuscles fall down, and the excess of fluid is quite obvious to the naked eye. This condition of the blood is very often observed in chronic nephritis as well. Some idea of the extent of the hydræmia can be ascertained by an estimation of the solids of a given volume of the blood or by hæmoglobin estimations. When such estimations are carried out it is usually found that a decrease of the water in the blood runs more or less parallel with a decrease in the blood pressure. The relationship between the rise of blood pressure and the hydræmia is of course complicated by such factors as the vasomotor tonus and the efficiency of the heart muscle, but on the whole it may be said that the hydræmia which is present appears in the great majority of cases to be closely connected with the rise in blood pressure.

Relation of Œdema to Hydræmia and Blood Pressure.

In a general way the œdema runs a parallel course to the hydræmia and blood pressure. Marked œdema, however, may be present with little or no hydræmia, while the latter may occasionally be present to a marked degree without œdema. The disappearance of œdema, hydræmia and high blood pressure is generally preceded and accompanied by an increase in the amount of urine secreted. Broadly speaking, a record of the daily body weight will indicate the extent to which the body is getting rid of excessive fluid, and it is found that there is usually a very close correspondence between the end of the period of raised blood pressure and the attainment of approximately constant weight. Several of these features are indicated on charts 1 and 2, from cases of acute nephritis. These charts are reproduced from "Special Series Reports," No. 43, of the Medical Research Council.

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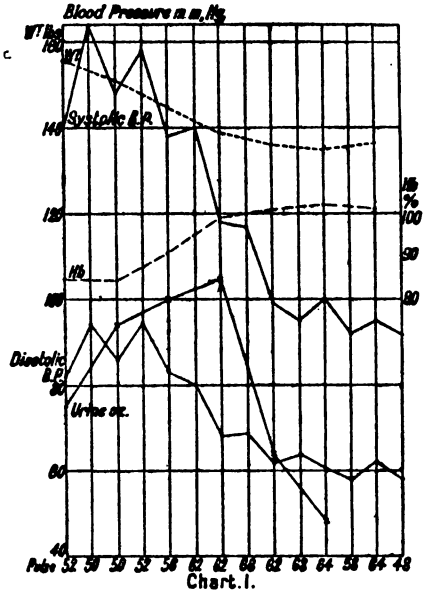

Chart.1.

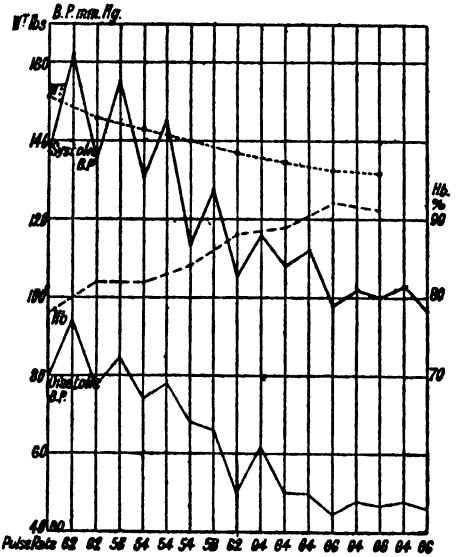

Chart.2.

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Condition of the Heart in Acute Nephritis.

Cardiac symptoms, so common in chronic nephritis, are by no means rare in the acute disease. Palpitation is often present after the fall of blood pressure, and periodical pain, varying in intensity from a slight feeling of contraction across the pericardium to short attacks of definite stabbing pain, may be noted. Precardial hyperæsthesia is sometimes complained of, but it is usually transitory. Another cardiac symptom is inability to sleep on the left side, attempts to do so being sometimes attended with precardiac pain and palpitation.

In some cases a temporary enlargement of the heart is present, so that the apex beat may be considerably external to the nipple line. This change in the size of the heart appears to be entirely dependent on the acute condition, and does not necessarily indicate the presence of chronic nephritis as well. Indeed, in the majority of favourable cases, the phenomenon is a very transitory one, the apex beat returning to the normal position within a few weeks; the recession is particularly marked after the blood pressure has fallen. The cardiac enlargement is generally seen in cases with marked œdema and hydræmia accompanied by high blood pressure, and is probably of the nature of a dilatation due to toxæmia and increased work. That a certain amount of hypertrophy is also present seems to be indicated by the changed character of the first sound at the apex. In all such cases the first apical sound is either more emphatic and louder than normal, or it may possess a distinct rumbling character. As a rule the impulse does not show the heaving character associated with a definitely hypertrophied heart, but it is usually vigorous and not diffuse. The condition is accompanied by a slow and full pulse. No evidence of right cardiac enlargement is usually obtained, and cardiac murmurs of all kinds are very rare. These changes in the heart during an attack of acute nephritis are important, for they are in some degree similar to what might be

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expected in chronic interstitial disease. The fact that they generally disappear in a few weeks proves that they have no relation to chronic disease, but an erroneous diagnosis of an acute attack grafted on to a chronic condition may be made if these points are forgotten.

Observations on Œdema and Polyuria.

In all severe cases of acute nephritis the amount of urine secreted during the early stages of the disease is notably diminished. This oliguria is accompanied by retention of urea and other nitrogenous products in the blood, so that even at an early stage the amount of urea in the blood may be relatively high. After a short time the usual course is for a marked polyuria to be established, but the cause of this has not been satisfactorily explained. When we consider, however, that urea is an excellent diuretic, a probable explanation is at once forthcoming. As soon as the kidney lesion improves to some extent and the organ is capable of excreting an increased amount of urine, the urea immediately exhibits its diuretic action, with the result that marked polyuria is set up. This continues until the excess of urea is eliminated. The excretion of urine is also helped by the increased blood pressure generally present during the stage of œdema. Indeed, all the factors conducive to increased excretion of fluid are present—increase of fluid in the blood, a raised concentration of urea in the blood and increased blood pressure. There is a good deal of evidence that the presence of a relatively large amount of urea in the blood tends to produce an excretion of fluid by kidneys damaged to such an extent that they do not respond materially to other factors; in this connection it is probable that the polyuria sometimes found even in moribund cases with a large accumulation of urea in the body tissues, may be due to the action of this retained urea.

With regard to the œdema, it is obvious that the retained fluid first of all tends to cause dilution of the blood, which, as already shown, is intimately associated, in the majority

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of cases, with a rise in the blood pressure. As this blood dilution increases the fluid naturally passes into the tissues. This takes place when the osmotic pressure of the blood proteins, already lowered by the dilution of the blood, is no longer able to counteract the tendency of the increased blood pressure to drive fluid into the tissues. When the kidneys begin to act, the concentration of the blood tends to be lowered, with the result that a reverse current is set up favouring the passage of tissue fluids into the blood and then into the urine. Indeed, all the processes encountered are such as might be expected on physical and chemical grounds. No doubt, the passage of fluid into the tissues may in certain cases be accelerated by damage to the capillary walls caused by the toxic processes which were responsible for the renal lesion.

The Chemical Findings in Acute Nephritis.

In general the chemical findings in the blood and urine run parallel with the clinical course of the disease, but in some instances the results of chemical investigation may be much less grave than the clinical manifestations appear to indicate. In such cases, experience suggests that the patient ultimately does much better than might have been expected from his condition during the earlier part of his disease. There is little doubt that very often a careful examination of the urine and blood yields most valuable information on which to base a trustworthy opinion as to the state of the patient and his immediate chances of recovery. The various methods which may be used in this connection are fully discussed in Chapter VI., but it may be mentioned that estimation of blood urea is one of the most valuable.

With regard to the urine, even in severe cases the excretion of urea is generally fairly good, though there is often a very much lessened total excretion during the earlier stages of the disease. In severe cases this retention of urea may be a very noticeable feature, while in mild cases it may be insignificant. As recovery takes place, a larger

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and larger amount of urea is thrown out per day, usually accompanied by an increase in the volume of urine. In some patients at this stage relatively large amounts of urea, corresponding to three or four times the nitrogen present in the diet, may be excreted for a few days, but the level soon falls. This excessive output is of course dependent on a previous accumulation of urea in the tissues. With regard to chlorides, it seems to be the rule for salt to be retained more or less during the earlier stages of the disease. In severe cases the urine may contain no salt at all to begin with, but as improvement sets in a small amount appears, and there is a gradual increase of this substance in the urine. As already explained, this retention of salt is intimately connected with the œdema. The return or increase of salt in the urine is one of the best and earliest indications of improvement in severe cases, and the test for chlorides should always be carried out. The results of daily examination of the urine in a case of acute nephritis are given below; they serve to illustrate the above points.

Case I.—A soldier aged 27 years, suffering from war nephritis, was admitted to hospital with headache, cough, œdema and dyspnœa. His pulse was full and regular, and the heart appeared to be of normal size. The œdema steadily increased for over a month. The urine contained protein, blood and casts of various kinds. The clinical course of the case strongly suggested the presence of chronic disease. On the other hand, as will be seen from a reference to the table, the chemical findings indicated a steady improvement in the renal condition, for the urea, and especially the chloride excretion, rose steadily. The diastatic reaction (p. 59) was also high, being about 20. This reaction supported the other chemical evidence suggesting that the case would terminate favourably, and this view proved to be correct, for after a month the condition improved and the patient became convalescent. The albuminuria, which was at first very severe, decreased steadily, and ultimately the urine contained only a small amount of protein. Casts which were also very numerous

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at the beginning, disappeared to a great extent. The findings with regard to amount of urine, total nitrogen, urea and chlorides passed per day for the first month after admission are given in the table. It will be observed that

TABLE 2.

Days after admission.	Urine in c.c.	Total nitrogen in grms.	Total urea in grms.	Total chlorides in grms.
1	558	7·59	14·82	Traces.
2	710	10·24	17·91	2·1
3	640	8·41	15·92	Traces.
4	970	—	—	Traces.
5	1,100	9·47	18·26	0·22
6	1,100	11·43	22·74	0·53
7	1,000	16·27	30·90	1·15
8	1,050	17·60	30·28	1·52
9	1,000	16·27	28·75	1·70
11	830	13·65	26·86	1·19
12	860	13·09	26·22	1·64
13	930	13·11	26·09	1·99
14	1,230	16·78	31·50	2·81
15	960	14·11	28·32	2·95
16	870	11·34	20·71	4·08
17	1,240	15·29	30·43	6·29
18	1,250	15·31	29·72	8·68
19	1,480	15·41	29·18	11·47
20	1,450	14·33	26·22	10·80
29	1,890	13·23	23·79	9·82
30	1,640	—	21·80	8·60

the total daily output of urea steadily increased from 14 grms. to a maximum of 31 grms. The chlorides, which at first, with the exception of one day, were present in mere traces, gradually increased to a maximum of 11 grms. per day and then slowly decreased. During this period the patient's daily diet did not contain more than 8 to 9 grms. of nitrogen, while the amount of chloride did not exceed 6 to 7 grms. The large increase in excreted nitrogen must therefore have been chiefly dependent on substances

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already accumulated in the body, and the same applies to the salt excreted at a later stage of the disease.

Eye Changes in Acute Nephritis.

Contrary to what is sometimes taught, definite eye changes are fairly common in certain severe cases of acute nephritis. During the epidemic of nephritis in the Great War many observers reported lesions of the fundus in a considerable percentage of cases. For instance, Bergemann, who carefully studied this aspect of the disease, states that 22 per cent. of his patients showed definite changes, which he summarised as follows: Retinal hæmorrhages, 10; retinal exudations, 23; exudations round papillæ, 3; retinal œdema, 56; choroiditis, 11; choked disc and old diseases of optic nerve, 3. In the majority of cases the lesions clear up without leaving any permanent damage. There is a certain amount of evidence pointing to the conclusion that these eye changes are connected with the raised blood pressure. The possibility of definite eye manifestations in acute nephritis must not be forgotten, since it is important to bear in mind that, unlike similar conditions in chronic disease, they are not necessarily of serious import, and do not constitute an important factor from the point of view of prognosis.

Convulsions in Acute Nephritis.

Convulsions, though not frequent in acute nephritis, are occasionally seen. Superficially they suggest uræmia, but they cannot be regarded as in any way connected with uræmia. They show a definite relationship to increased blood pressure, and it is probable that they are really vascular in character. The blood urea is often not increased in amount in such cases, while in true uræmia it is practically always raised. Unlike uræmic fits, they seldom, if ever, terminate fatally in an uncomplicated case, and are not to be regarded seriously. In fact, some observers hold the opinion that they rather tend to indicate a good prognosis as to speedy recovery. Treatment con-

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sists in removing 20 ounces or so of blood from the patient. According to some, lumbar puncture is also of service.

Chronic Nephritis.

Chronic nephritis may be the result of acute nephritis, or may apparently develop as the result of vascular or toxic changes in patients who have never had a history of an attack of acute nephritis. The usual form of chronic nephritis is associated with degeneration of the renal cells, and is accompanied by marked interstitial changes in the kidney; hence it is generally referred to as chronic interstitial nephritis. The degree to which the various processes have progressed defines, in a rough way, the gravity of the symptoms of this disease. These symptoms, as is well known, may vary from ill-defined feelings of apparently little importance to definite uræmic manifestations. It is no part of this small volume to discuss the symptoms of chronic Bright's disease, but the following general observations may be of value in making clear certain points which are discussed later. Various attempts have been made to correlate the *post-mortem* histological findings in the kidney with the symptoms during life. So far, these attempts have failed, and the clinical findings have often not been easy to correlate with the histological changes. Far too much attention has been paid in the past to gross macroscopic appearances in the kidney. After all, it matters little whether a kidney is found to be large or small, white or red, rough or smooth, soft or hard. What is really of importance is to ascertain to what extent the renal functions are interfered with during life, and it appears to the writer that little is to be gained by a more or less artificial grouping based chiefly on the naked eye appearances of the organ after death. On the other hand, a careful attempt to correlate histological appearances with the clinical condition, as indicated by functional tests, would probably yield fruitful results.

Since no satisfactory classification of chronic renal disease has ever been made, it is much better, especially

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from the clinical standpoint, to consider these chronic conditions solely from the point of view of renal function. When this is done, chaos gives place to comparative order. Now the extent to which the kidney functions are interfered with varies much in different cases, and consequently the symptoms may also vary, but, broadly speaking, there are two chief types of chronic disease, one of which is characterised by a tendency to retain nitrogenous products, while the other is associated with retention of salt. In the first type the kidney has some difficulty in eliminating the waste products of nitrogenous metabolism already described, and so there is a tendency for an increase of these substances in the blood. This is the usual type of chronic renal disease generally called "chronic Bright's disease" or "chronic interstitial nephritis." To avoid confusion with histological findings, however, it is best to refer to this type of case purely with reference to the renal function of eliminating nitrogenous waste. Following the French school, we may call it the *azotæmic type*.

The other variety of chronic disease is of comparatively rare occurrence, and is characterised by a failure on the part of the kidney to excrete salt. This defect is associated with marked œdema and ascites (p. 11), and represents the condition generally referred to as "chronic parenchymatous nephritis." Since its chief characteristic is an accumulation of fluid in the system, we will refer to it as the *hydræmic type*.

Azotæmic Type of Chronic Nephritis.

By far the greater number of all cases of chronic nephritis come under this heading. At an early stage there may of course be no actual increase of nitrogenous waste products in the blood, but the tendency is in this direction, and, sooner or later, as the malady progresses, evidence of defective renal action is found in an increased concentration of blood urea and other substances. This is the class of case in which the cardio-vascular system so often shows the well-known signs of degeneration. In the more

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advanced stages of the disease the concentration of the urea in the urine is decreased, and the patient passes a urine of low specific gravity. Often there is no œdema, and the urinary protein may be only moderate or slight in amount. Indeed, it is not very uncommon to find a patient with very advanced disease whose urine contains either no protein at all or only a small amount at infrequent intervals. Strange to say, there is usually no difficulty in eliminating salt or water, and consequently œdema is not a prominent feature. As discussed later, the amount of protein present often bears no relation to the severity of the disease, and the same statement applies in a general way to casts as well. This is the type of renal disease in which the various tests for kidney efficiency give such useful information. In examining a patient for renal efficiency one always examines for disease of this nature, as the hydræmic variety, to which reference has been made, responds normally to these tests. The azotæmic type of disease frequently terminates in death from uræmia.

Hydræmic Type of Chronic Nephritis.

The term "hydræmic type" is used solely from the point of view of chemical findings. In this type of case there appears to be no difficulty in excreting nitrogenous bodies, but the urine contains little or no sodium chloride. Consequently, the disease is always characterised by one very important symptom—œdema—which may be very extreme. Usually the urine contains a very large quantity of protein and numbers of casts, the hyaline variety often predominating. Although, as already indicated, the usual renal tests are not of much value in the investigation of uncomplicated cases of this nature, no tests are really required, for the great retention of fluid in the body renders the condition obvious.

Not infrequently the symptoms of both azotæmic and hydræmic disease are present in the same patient, but more often very definite findings of one or the other variety may be obtained. When, therefore, we come across a patient

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with very marked ascites and œdema, we often find on examination, by the tests to be described later, that the renal functions seem to be fairly normal. The only defect appears to be in the elimination of salt. Albuminuria is extreme, and few or no cardio-vascular changes are in evidence. Such a case would be taken as a good example of the hydræmic type. On the other hand, it might be found that a patient with œdema showed an increase of blood urea and gave low values with the other functional tests; marked cardio-vascular changes might also be present. Such a case would be an example of the azotæmic variety. Indeed, if a patient survives for a year or two, the pure hydræmic case soon shows symptoms of the azotæmic variety as well, so that, sooner or later, such cases furnish symptoms of both varieties of disease. This is more fully discussed in Chapter IX.

This classification is entirely based on certain findings when the patients are examined by chemical tests. Its conception is exceedingly simple, and it furnishes a useful basis from the clinical standpoint. For practical purposes, nearly all the cases we see come under the azotæmic type, and the extent of the disease is indicated by the usual tests. Hydræmic nephritis can never be present in the absence of œdema or ascites. The chief differences between the two forms of the disease in typical cases are as follows:

Interstitial Nephritis.	*Parenchymatous Nephritis.*
(1) Œdema absent.	Œdema present.
(2) Protein usually present in urine, but often slight or moderate in amount.	Protein present in urine, often in very large amount.
(3) Chlorides present in normal amount.	Chlorides diminished or may be absent.
(4) Urea concentration (urinary) decreased.	Urea concentration normal.
(5) Tendency to increase of urea and other nitrogenous products in the blood.	No retention of nitrogenous products in the blood.
(6) Cardio-vascular changes marked.	Cardio-vascular changes absent or slight.
(7) Tendency to uræmia.	Uræmia less frequent.

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CHAPTER III

THE SIGNIFICANCE OF ALBUMINURIA AND CASTS

For many years after Bright pointed out the connection between albuminuria and disease of the kidneys the presence of protein in the urine was looked upon as a sign of grave significance. Gradually, however, evidence accumulated which seemed to indicate that not all patients suffering from definite albuminuria were the subjects of renal disease, but it must be allowed that, even up to the present time, too much importance has been attached to this condition. Leaving out of account such causes of albuminuria as pus, spermatozoa, secretions from the urethra, etc., it is now well recognised that temporary albuminuria may be the result of various factors, such as severe and sustained exercise, cold bathing and the taking of certain drugs.

Another well-recognised form of albuminuria, very common in young people, is that sometimes referred to as "physiological albuminuria" or "albuminuria of adolescents." This condition leads to no ill effects, and has nothing whatever to do with renal disease. In the majority of cases it clears up entirely in after-years, and, so far as is known, has no deleterious effect whatever either on the kidney or on the patient in general. Many theories have been advanced to account for this albuminuria of adolescents, among the most prominent being the suggestion, supported by Pavy and others, that it depends on mechanical conditions of the circulation. This view is in agreement with the well-known fact that the albuminuria is often absent during rest, and returns when the patient assumes the erect posture. The presence of general cardiac and vasomotor irritability, so often observed in this condition,

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is also suggestive. According to Sir Almroth Wright, the fault lies in the blood. He attributes the condition to a deficiency in the coagulating power of the blood brought about by abnormal calcium metabolism. Acting on this theory, calcium chloride has been administered with beneficial results in some cases; it is not always successful, however, even when large doses are employed. The subjects of this form of albuminuria are generally quite young with good general health. In many cases there has been rapid body growth, and the individual has often a "weedy" appearance. There is a tendency for the blood pressure to be rather low, though often it may be quite normal. The patient is generally more or less excitable, and the heart's action abnormally responsive to a slight stimulus. The albumin present may be in moderate quantity, and the amount very rarely exceeds 1 to 1·5 per cent. The urine passed in the morning after a night's rest is very often free from protein, or at most only traces are found. A peculiar and not uncommon feature is the presence of calcium oxalate crystals. Casts are generally absent, though a few hyaline or even epithelial ones sometimes may be observed. With the exception of the albuminuria, no signs of renal disease, such as dropsy, cardiovascular involvement, or headache, are present. In some cases the protein contains a larger proportion of globulin than is generally present in renal disease, but too much importance must not be attached to this phenomenon. The presence of globulin can be easily determined by the addition of a few drops of 30 per cent. acetic acid to half a test tubeful of the urine. A white precipitate occurring immediately after the addition of one or two drops or more of the acid indicates globulin; this precipitate is soluble in excess of the reagent. Various claims which are not borne out by experience have been made for this simple test. The examination of many thousands of cases of chronic nephritis proves that a globulin reaction is not rare even in advanced cases of renal disease. In young people, however, whose urine contains protein and in

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whom the absence of other features of renal disease suggests a diagnosis of "albuminuria of adolescents," the presence of a large amount of globulin perhaps tends to confirm the diagnosis. In all suspected cases, however, the only satisfactory method is to test the patient by the various means described later. In the great majority of such cases these tests will help to decide definitely what the condition of the kidney really is. Young patients suffering from albuminuria are quite common in the experience of every practitioner, and often cause a good deal of anxiety as to the prognosis. That this particular form of albuminuria leads to no bad after-effects is proved by the work of several investigators. One of the most conclusive and interesting observations on this point was carried out by Dr. Hingston Fox, who in a paper read to the Assurance Medical Society in November, 1920, described the after-testing of 20 patients who had albuminuria of this type when examined previously for life assurance. Of the 20, 4 died—(1) after 7 years, of phthisis; (2) after 7 years, of accident; (3) after 25 years, of senile decay and cardiac failure following accident; (4) after 32 years, of chronic arthritis. Three others were last heard of at periods of 16 and 15 years after entering; they were then believed to be healthy. Of the remaining 13, information was available up to November, 1920. They were all living at that date. The average period since the albuminuria was described in these 13 cases was 30 years. So far as known, they were all healthy persons at the time the communication was made. It is interesting to note that no evidence appears in the after-testing of these cases, prolonged in some of them for more than 30 years, of any subsequent renal disease. Among other observations those of Dr. Clement Dukes, carried out on Rugby scholars about 40 years ago, gave valuable results. Dukes examined later in life the urine of individuals who had albumin while at Rugby, and in only one case was the condition found to persist. He came to the conclusion that this albuminuria was not likely to

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give rise to organic disease of the kidneys in after-life. Various other observations have been made, but the above suffice to show that the condition is harmless.

Albuminuria in the Adult Population.

Though this albuminuria of adolescents is well known, little information of the general incidence of albuminuria in the ordinary adult population is available. Attempts to examine inmates of institutions have been made from time to time, with the result that the number of persons showing albuminuria was generally surprisingly large. An opportunity of ascertaining the incidence of albuminuria in a very large number of soldiers serving in France occurred during the War, and the results obtained indicate beyond dispute that albuminuria is much more common in the adult population than was formerly believed. A detailed investigation which was carried out by the writer is contained in a report entitled "Albuminuria and War Nephritis among British Troops in France," issued by the Medical Research Council. The primary object in undertaking this investigation was to ascertain whether soldiers suffering from albuminuria were more liable to suffer at a later period from war nephritis than those whose urines were normal in this respect. This war nephritis was practically always contracted while the soldier was serving in the front area, very few cases occurring during the preliminary training. In each case of nephritis that appeared one was always confronted with the question, Has he had some kidney defect previously, and is his present attack merely an exacerbation brought on as the result of the conditions of warfare, or has it arisen *de novo?* In the majority of cases an answer could not be furnished by any clinical observations made on the patient while actually suffering from the disease, for the problem of pre-existent renal trouble is a most difficult one and often incapable of solution. Renal disease may be present with few or no clinical symptoms, while, on the other hand, it is now acknowledged that an acute attack may in a short

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time give rise to certain cardiac and other changes strongly suggestive of chronic disease.

If, however, it were found that the great majority of war nephritis cases were suffering from albuminuria when examined at an earlier period, then one might say with confidence that war nephritis was probably dependent on a pre-existent kidney lesion, which, though perhaps originally very slight in degree, yet ultimately gave rise to an acute inflammatory process, as a result of the necessary exposure and fatigue of the campaign. More interesting still from the civilian point of view, such a finding would indicate that albuminuria, even in the absence of any other signs of renal disease, must often be associated with unsuspected renal deficiency or inadequacy which rendered the kidneys liable to disease. It was found, however, that only a very small percentage of men admitted to hospital suffering from nephritis showed any albuminuria some months earlier. It was also definitely established that men who showed albuminuria were no more liable to contract nephritis at a later period than were others whose urine was albumin-free. In short, there was no relationship whatever between pre-existing albuminuria and war nephritis, so that, as far as the evidence went, it pointed strongly to the conclusion that albuminuria *per se* did not predispose to nephritis under conditions that would be likely to bring out any latent defect in the kidneys. This result supports the evidence already brought forward as to the harmlessness of adolescent albuminuria. It is now certain that albuminuria may be present in individuals up to 40 or 45 years of age, at any rate, without having any morbid significance whatever; a similar condition is also often seen in the aged.

Incidence of Albuminuria in the Army.

In the investigation mentioned, 60,000 men were examined. Of these 10,000 were examined at Aldershot immediately after joining up, while the remainder were seen at Etaples after they had completed their training

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and immediately before going to the front line. In both groups the incidence of albuminuria was practically the same, indicating that training had no effect on its production. After allowing for pus, spermatozoa, etc., 5 per cent. of the men examined showed albuminuria for which no cause could be ascertained. In 2 per cent. the albuminuria was very marked, while in 3 per cent. it was slight. This large incidence of albuminuria in apparently healthy men was quite unexpected; as far as could be ascertained, no other signs of renal disease were present, nor did the condition interfere in any degree with the men's activity. It should be mentioned that all the samples of urine were collected immediately after the men got up in the morning, so that the incidence found was probably smaller than would have been the case had the urines been collected during the day. In one experiment carried out on 200 men to ascertain the effect of exercise, the incidence of albumin increased from 7 per cent. to 14 per cent. It is, therefore, obvious that albuminuria is much more common in the adult population than is generally supposed, and that its presence may be determined at any given time by accidental features, such as exercise taken immediately before the examination is made.

Presence of Casts in Albuminous Urine.

All the specimens of urine which contained albumin were examined for casts. Almost all the casts found were either epithelial or hyaline; very few blood casts were encountered. The epithelial casts varied much in the stage of degeneration presented by the epithelium, but the majority of them presented the usual appearances seen in acute nephritis, where the outline of the individual cell is often fairly distinct. The hyaline casts also comprised many of the ordinary fine ill-defined variety, but a considerable number were definitely granular in structure and might be referred to as hyalo-granular casts. For purposes of reference the casts were divided into two classes: epithelial and hyaline. Many authorities believe that

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the presence of epithelial casts—at any rate in moderately large numbers—is pathological and indicates some definite lesion of the kidney, while there is a tendency to regard the hyaline variety as of little significance. Experience shows, however, that both varieties of casts may be present in cases where the kidney seems to be quite efficient, while few or none may be found even in grave renal lesions. On the whole, the epithelial cast is perhaps the most significant, but the presence of albuminuria and a few epithelial casts is no proof that we are dealing with defective kidneys. Of the albuminous urines described above, nearly half of those with a large amount of albumin contained either epithelial or hyaline casts or both, while only 20 per cent. of urines with a small amount of protein showed casts. In many cases, only very few casts were found. For the 50,000 men examined the average percentage of urines found to contain casts was 1·87; of this number 0·84 per cent. had definite epithelial casts, while in 1·03 per cent. hyaline casts only were found. In examining for casts the centrifuge was always used.

In a considerable number of urines containing casts the diastatic test (p. 59) was employed. With the exception of a very few cases, the diastatic reaction was between 15 and 25—figures practically identical with those obtained from normal urine. The albuminous urines from 10,000 cases were tested by means of acetic acid for globulin, but in only a few cases was a definite reaction obtained (see p. 33).

General Observations.

Albuminuria is by no means a rare condition, and is often found in the absence of renal disease. Even when accompanied by casts, there is no proof that the patient is suffering from defective kidneys. On the other hand, advanced renal disease may be present without albuminuria. Even in patients who formerly suffered from acute nephritis, the persistence of protein in the urine is no indication that the disease is progressive, for there are

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undoubtedly cases where marked albuminuria is found many years after the initial attack, yet the patient enjoys perfect health, and no deficiency of the kidneys is indicated by the usual tests for renal inefficiency. In every case of albuminuria it is therefore essential to have the kidneys examined by these tests. Very often it will be found that no defect whatever can be ascertained. The knowledge that a patient suffers from albuminuria does not help us much ; it may be of serious import, or it may be insignificant. In the absence of symptoms pointing to renal disease, it is usually a condition of no importance, but each case must of course be judged on its merits.

In all these cases we must never forget the possibility of some rare condition such as a gumma or tumour of the kidney, but careful investigation of the history and the clinical condition should, in the majority of cases, help us to avoid pitfalls of this nature. In spite of the greatest care on the part of the examiner, an occasional mistake of this kind will be made, but such mistakes should be exceedingly rare if the necessary care is taken, and they should be regarded as exceptions having no bearing on the general rule that albuminuria *per se* is generally of little consequence. Albumin associated with blood or pus in the urine is, of course, in another category altogether, and such a condition should never be regarded as an ordinary albuminuria of adolescents. The presence of pus usually signifies either urethritis or pyelitis, and in the latter case the possibility of calculus must never be overlooked. In all those cases the examination of the deposit is of very great importance and should never be omitted, as it is impossible to give a diagnosis unless this point has been carefully attended to ; in the not uncommon case of pyelitis from calculus the amount of albumin is generally small.

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CHAPTER IV

BLOOD EXAMINATION IN RENAL DISEASE

Of all renal tests, the most important in acute or chronic conditions in which the renal functions are grossly interfered with, is the estimation of the retained nitrogenous bodies in the blood. As already indicated, the chief of these nitrogenous bodies are urea, uric acid, creatinin and purin bodies; the term "non-protein nitrogen" is generally used to express the total nitrogen derived from these substances, and this non-protein nitrogen may be estimated. This, however, is a somewhat lengthy and difficult process, necessitating care and some technical skill if the results are to be depended on. Quite as much information is to be derived from the much simpler process of estimating the urea present, and the rapidity and ease with which this procedure can be carried out renders it of great value in renal work. Personally, in routine work, when a blood examination appears necessary, I always estimate the blood urea, and have never obtained any additional help from an estimation of the non-protein nitrogen as well. Certain observers claim that the separate estimation of urea, uric acid and creatinin gives additional information, since there is some evidence which appears to indicate that the first substance to accumulate in the blood in cases of chronic nephritis is uric acid; after this urea is retained, and still later creatinin. Various American authorities have found that patients suffering from chronic nephritis whose blood contained more than 5 mgrs. creatinin (as against a normal value of 1 to 2·5 mgrs.) all died in a short time. No doubt, when the blood creatinin rises to 5 mgrs. or over, the outlook is generally bad, but the writer has seen patients in whom the creatinin

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was considerably higher than this, and yet these patients were alive at least two years afterwards. For research work the separate investigation of these different bodies is valuable, but for clinical purposes such estimations are superfluous.

Importance of Blood Urea.

Under ordinary conditions the blood always contains a certain amount of urea, but the exact amount which may be considered to represent the normal value is still not agreed upon. As the result of a very large number of experiments, I have come to the conclusion that the blood of normal individuals may contain from about 15 to 40 mgrs. urea per 100 c.c. blood. In young people the normal content lies towards the lower value, and perhaps the maximum should be placed somewhere below 30 mgrs., but in elderly people with apparently healthy kidneys, it is not uncommon to find a blood urea content of 40 mgrs. or even a little more. These figures refer to individuals on average ordinary diets. Anything over 40 mgrs. is suspicious, and when it rises to 50 mgrs. or over we may under ordinary circumstances be fairly certain that the kidneys are inefficient. Certain conditions, such as severe vomiting and diarrhœa, may so deplete the body of fluid that even healthy kidneys fail to maintain the blood urea within its normal limits, but such cases are comparatively rare. An increase in blood urea is sometimes seen in cardiac disease, but it is generally not difficult to ascribe it to its true cause (see Chapter VI.).

Blood Urea increased only in Bad Cases.

While the test is of very great value in many cases, it unfortunately gives no indication of kidney defect in subacute and chronic cases of Bright's disease until the greater part of the renal tissue is out of action. Animal experiments have shown that three-quarters or so of the total kidney substance may be removed before any accumulation of urea or non-protein nitrogen is found in the blood.

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Chronic cases with high blood urea give, as a rule, little trouble from the point of view of diagnosis and prognosis, for various other symptoms indicate the state of the kidneys with sufficient clearness. It is true that there are exceptions, but, on the whole, one can often tell beforehand on clinical grounds alone that certain patients have a raised blood urea content.

Uræmia not due to Urea.

It is important to note that the excess of urea or other nitrogenous constituents in the blood is not the cause of the symptoms from which the nephritic suffers, and it appears certain that urea has nothing to do with the production of uræmia. It is generally not very difficult to reduce the blood urea even in advanced cases of chronic interstitial nephritis, by giving a diet largely composed of carbohydrates, but this does not relieve the patient. In one such case under my charge the blood urea was reduced from 120 mgrs. to an average of 30 to 40 mgrs. per 100 c.c. blood, but though the blood urea was maintained at this lower level for a considerable period, the patient died of uræmia; his blood urea on the day before death was 30 mgrs.

The point to note is that a lowering of the blood urea is not necessarily any indication of improvement unless the patient continues on the same kind of diet as he had when the blood urea was found to be high. This unfortunately is frequently forgotten.

Mechanism of Urea Excretion.

In considering the mechanism of urea excretion, it is useful to remember that a patient suffering from even an advanced grade of chronic interstitial nephritis excretes practically the same amount of urea *per diem* as does a healthy individual on a similar diet. This seems absurd, but of course it is obvious, for if this were not the case, the patient would soon become saturated with urea. There is, however, a marked difference between the mode of excretion in the normal and nephritic subjects. The normal

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individual requires what we may term a "head" of 20 mgrs. or so of urea per 100 c.c. of blood in order to get rid of the 25 or 30 grm. excreted daily in the urine; the nephritic, though he excretes as much urea in the urine as the healthy individual, can do this only when the "head" of urea in the blood is much higher, and this head may amount to 200 mgrs. per 100 c.c. of blood or even more. The blood urea content is therefore merely an index of the efficiency of the kidney, and when nitrogenous food is largely withdrawn from the diet the necessary amount of urea can be got rid of in the urine with a smaller head of urea in the blood. Even on the same diet, one finds variations in blood urea in chronic cases, so that before expressing an opinion as to prognosis more than one estimation should be carried out.

Cases in which Estimation of Blood Urea is indicated.

In acute cases estimation of blood urea at periods of a week or 10 days is one of the best methods for estimating the progress of the disease, and in a general way the same applies to subacute conditions. On the whole, the estimation of blood urea is of very great help in acute and subacute cases of nephritis and in advanced cases of interstitial nephritis, but, in the latter especially, the results must be used with great care and discrimination. Generally, an increase in urea or non-protein nitrogen of the blood indicates that the kidneys are defective in proportion to the amount of these bodies present, but the occurrence of what must be accepted as acute or subacute exacerbations in chronic cases must not be forgotten. Such exacerbations appear to be of frequent occurrence in patients suffering from renal disease secondary to cardiovascular trouble. In one case of this kind, the patient had frequent attacks of mild dyspnœa and general malaise, during which his blood urea reached 150 to 180 mgrs. per 100 c.c. His urine always contained protein and epithelial casts. I first examined him three years ago, when his blood urea was 180 mgrs. On the whole, the prognosis seemed

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to be bad. When I last examined him, his blood urea was 45 mgrs., and he felt much better. At various intervals between, the blood urea was sometimes high and sometimes as low as 50 mgrs. In one other type of case, which I shall refer to more fully later on, estimation of the blood urea is of very great importance. I mean the type of renal involvement associated with certain genito-urinary diseases, such as enlarged prostate, in which surgical interference may be necessary. On the whole, the estimation of urea or non-protein nitrogen in the blood is one of the best tests we have for advanced renal deficiency, but the results must be interpreted with care, and the clinical symptoms must, of course, never be forgotten.

Method of Estimation of Blood Urea.

The estimation of the blood urea is carried out on the lines suggested by Marshall, Van Slyke and many others. The slight modifications here described were suggested by MacLean and de Wesselow, and have been found to work well.

The principle of the method depends on the fact that soya bean contains a specific enzyme (urease) which converts urea quantitatively into ammonium carbonate, but has no effect whatever on any other nitrogenous constituent. In the presence of alkali, the ammonia is liberated from the ammonium carbonate, and, by the help of a current of air, is passed through a standard solution of acid. The amount of acid neutralised indicates the amount of ammonia present, and from this the urea can be calculated. Various preparations of urease, more or less pure, are now on the market, but they all suffer from the disadvantage that they are unstable, and therefore soon become unreliable. For clinical work it is far better to use finely ground soya bean meal; this can be prepared by passing the beans through a coffee machine, and it keeps for some time. For each experiment 0·3 grm. of this meal is used, but, since it contains traces of ammonia, a small allowance has to be made. In various specimens 0·3 grm. of the meal

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neutralised almost exactly 0·4 c.c. N/100 sulphuric acid. This has to be subtracted from the total amount of the acid neutralised in the actual experiment.

The estimation is carried out by means of tubes fitted as shown in Fig. 1.

These tubes should be about 200 mm. deep and about 25 mm. wide. Each tube has a well-fitting rubber cork. Through this cork two small tubes pass. One of these (N) has a small dilatation at the end, which is perforated with several small holes. This tube goes to the bottom of the larger tube (A). Through the other hole passes a tube (M) with a dilatation, which acts as a trap to prevent any fluid passing over. Two such large tubes are required for each estimation. To each of the small tubes passing through the rubber stopper is attached about 1 foot of ordinary stethoscope rubber tubing (P). For the accurate measurement of the blood it is best to have a special pipette made " to contain " 3 c.c.

The materials required to carry out an estimation are as follows :—

(1) A solution containing 6 grams potassium hydrogen phosphate in 1 litre of water.

(2) Soya bean meal.

(3) Caprylic alcohol (to prevent frothing).

(4) N/100 sulphuric acid and N/100 sodium hydroxide solutions.

(5) A saturated solution of methyl red in 50 per cent. alcohol (indicator).

(6) Solid anhydrous potassium carbonate.

(7) Saturated solution of potassium carbonate.

(8) 2 × 25 c.c. burettes accurately graduated in tenths.

(9) A pipette made to contain 3 c.c. blood (supplied by Hawksley & Son, Wigmore Street, W.).

(10) A good water suction pump.

Method of obtaining Blood.

About 10 c.c. or less of blood are withdrawn from a vein at the bend of the elbow into a test-tube, coagulation being

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prevented by the use of a small amount of finely powdered potassium oxalate. Immediately on withdrawing the blood, the tube containing it must be inverted a few times to mix the solid oxalate thoroughly with the blood, otherwise coagulation may take place.

Details of Actual Estimation of Urea.

Tubes fitted as above described (see Fig. 1) are taken and adjusted so that the perforated inner tube with the small bulb passes to the bottom of the outer tube. One of these tubes (B) is used for the blood, while another (C) serves to contain the acid required for estimating the ammonia. The rubber corks with their attachments are then removed and 5 c.c. of acid sodium phosphate solution measured into the blood tube. By means of the special pipette 3 c.c. of blood are added to the phosphate, the pipette being thoroughly washed out two or three times with the phosphate mixture, so as to remove all traces of blood. From 6 to 8 drops of caprylic alcohol are then added, and finally 0·3 grm. of soya bean meal. The rubber stopper is now quickly replaced and the tube closed by means of clips on the rubber tubing. The tube is placed in a bath at a temperature of 40° to 45° C. and left there for 10 to 15 minutes. During this time it should be occasionally shaken. While the urease is acting on the blood urea 25 c.c. of N/100 acid are added to the other tube (C) together with 1 drop of caprylic alcohol and 2 drops of methyl red solution.

When hydrolysis of the urea is complete the blood tube B is removed from the bath and connected on the one side with tube A, which contains some 5 per cent. H_2SO_4, and on the other side with the tube C, which contains the 25 c.c. of N/100 acid, exactly as shown in the figure. The clips are now opened and air drawn through the whole system for 2 minutes or so by means of a suction pump connected at S. The air entering at N first passes through the 5 per cent. H_2SO_4, which removes any traces of ammonia that may be present. It

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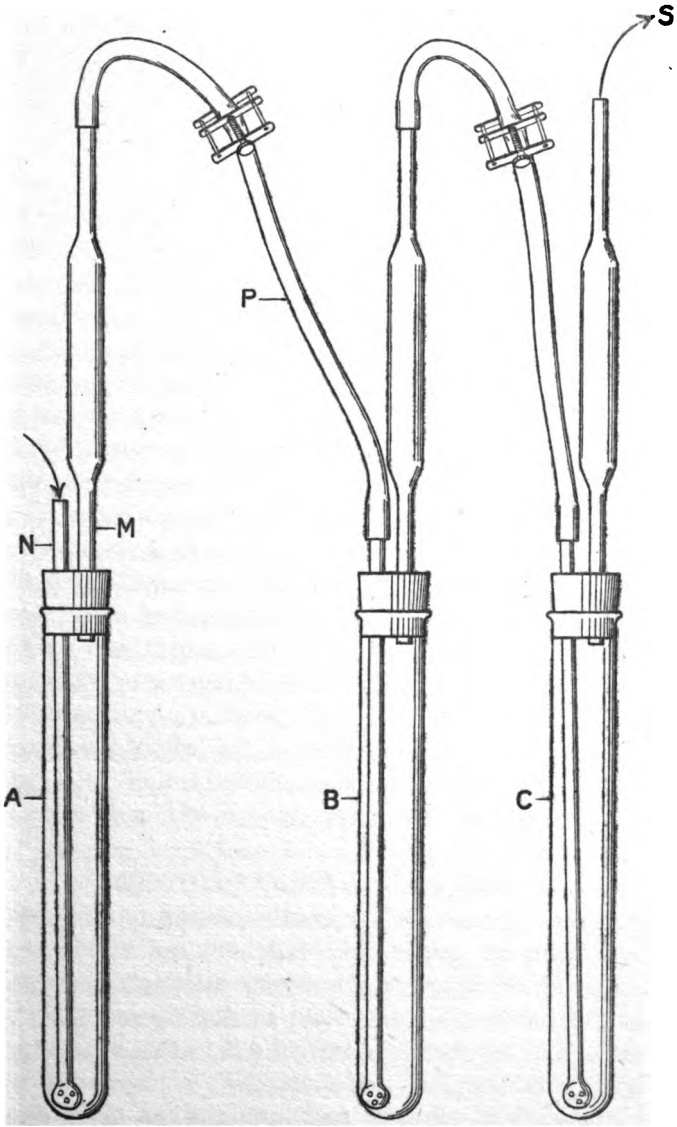

FIG. 1.—Arrangement of tubes for estimation of blood urea. A contains 5 per cent. H_2SO_4. B contains blood. C contains 25 c.c. N/100 H_2SO_4. S leads to suction pump.

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then passes through the blood, and finally through the N/100 acid, which takes up any ammonia carried over from the blood. After 2 minutes, suction is stopped, the blood tube B opened and 4 c.c. of saturated potassium carbonate solution, followed by 3 grm. of solid anhydrous potassium carbonate, quickly added. The stopper is immediately replaced and a current of air drawn through; this should be slow at first, but after a few minutes the pump may be turned on to its fullest capacity. The time required for the complete removal of the ammonia depends on the pump employed, but with an ordinary pump the experiment should be complete in 30 minutes.

The tube containing the standard is now disconnected and the acid transferred quantitatively to a small Erlenmeyer flask. To do this the tube and the perforated bulb must be washed two or three times with small quantities of distilled water. The acid is then titrated with N/100 sodium hydroxide until the indicator gives a faint yellow colour. The difference between the 25 c.c. acid originally taken and the number of cubic centimetres of alkali used gives the number of cubic centimetres neutralised by the ammonia. From this 0·4 c.c. must be subtracted to allow for traces of ammonia generated from the soya bean.

The calculation is very simple, for when the above quantities are used each cubic centimetre of acid neutralised equals 10 mgrs. urea per 100 c.c. of blood.

Estimation of Non-protein Nitrogen.

For the methods of estimating the non-protein nitrogen of the blood we are chiefly indebted to Folin. The process described here has given very satisfactory results, and is essentially Folin's method as slightly modified by Greenwald. The process is carried out in two operations, which may be described as follows:—

(1) Removal of protein and preparation of a clear filtrate from blood.

(2) Estimation of nitrogen in aliquot part of filtrate by modified Kjeldahl's process.

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Preparation of Clear Non-protein Filtrate from Blood.

To 3 c.c. blood diluted with 12 c.c. distilled water are added 15 c.c. of a 10 per cent. trichloracetic acid solution. After thorough mixing, this is allowed to stand in a closed vessel for half an hour; it is then filtered through a small filter paper and a water-clear filtrate obtained. The filtration is slow, but over 20 c.c. should be ultimately procured.

Estimation of Nitrogen in Filtrate.

For the estimation of the nitrogen a tube similar in size to that used for urea is required. This tube must be made of Jena, Pyrex or other hard heat-resisting glass. Into this tube are introduced 10 c.c. of the above filtrate, together with 1 c.c. pure concentrated sulphuric acid and 3 drops 5 per cent. copper sulphate solution. To prevent bumping, 0·1 grm. finely ground pumice and two or three very small beads are also introduced. The mixture is boiled until the excess of water is removed. To prevent loss of material, it is necessary to keep the tube in a slanting position and to use a very small flame, as there is a tendency for bumping to take place. When the total bulk is reduced to about 3 c.c. the tube is placed in the upright position and heated until the material begins to char. The position of the tube in the vertical direction ensures that the sides are well washed down. At this stage 0·3 grm. of potassium sulphate is added and heating continued for 15 minutes after the mixture clears. Owing to the presence of pumice stone, the fluid never becomes quite transparent, but, in spite of this, it is quite easy to ascertain when the reaction is completed. The mixture is now allowed to cool, but while it is still warm 6 c.c. of distilled water are added; it is then cooled under the tap and is ready for distillation of the ammonia. For this distillation an arrangement exactly similar to that described for urea is used, the ammonia being liberated by the addition of 3 c.c. saturated potassium hydroxide solution. To prevent any escape of ammonia during the

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addition of the alkali, an inner tube (Fig. 2) graduated to contain 3 c.c. up to the mark is used. By sucking up the caustic potash solution to the mark and closing by a clip the rubber tube M attached, the alkali remains in this tube until the clip is released. The rubber attached to the short tube N is now closed with another clip, and the inner tube, containing the potash, inserted into the larger tube, as shown in the diagram. The rubber tubes are now attached to a tube containing a 5 per cent. solution of sulphuric acid on the one side and to one containing 25 c.c. of a standard solution of N/100 H_2SO_4 on the other, exactly as shown for blood urea (Fig. 1). The suction

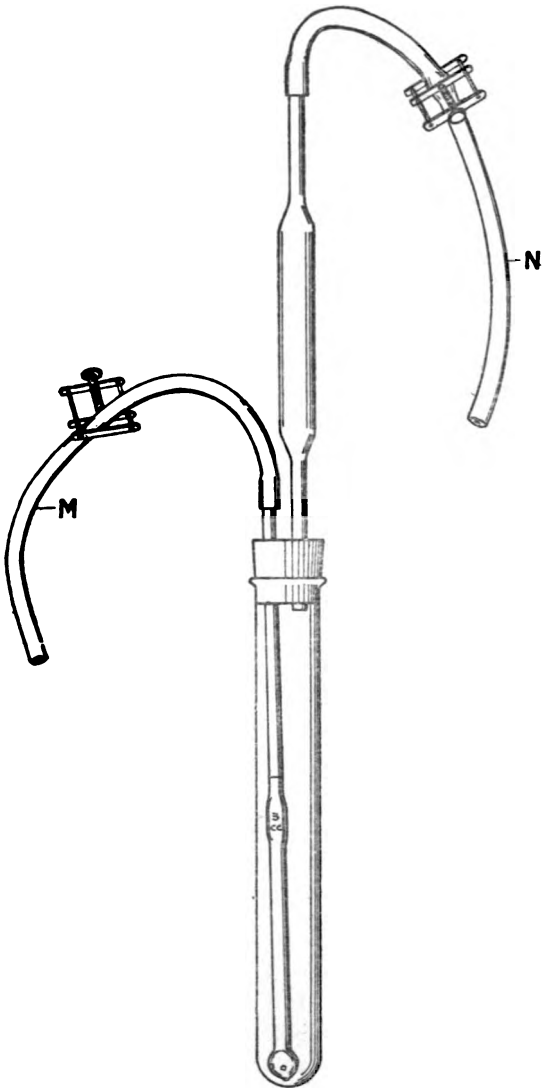

FIG. 2.—Arrangement for distillation of ammonia in estimating non-protein nitrogen of blood.

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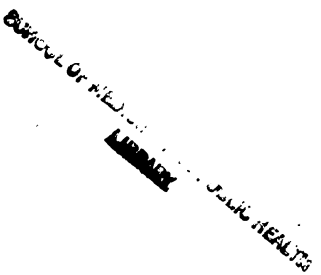
pump is attached to the tube with the standard acid. The alkali is then allowed to mix with the solution in the large tube by unscrewing the clip on the rubber tube M, but before doing this the clip N must be opened. Aeration is then started and continued for half an hour; for the first five minutes this aeration should be comparatively slow, but after that the pump can be turned on to its full extent. Titration with N/100 NaOH is carried out as in the estimation of blood urea, a blank equivalent to 0·15 c.c. N/100 H_2SO_4 being allowed for the chemicals used.

1 c.c. N/100 H_2SO_4 = 0·00014 grm. nitrogen.

Like urea, the non-protein nitrogen varies considerably in different individuals, but the average amount is generally given as about 25 to 30 mgrs. per 100 c.c. of blood. In elderly people it may be somewhat in excess of this amount.

The tubes used for this process should be kept filled with absolute alcohol when not in use, for if this is not done, bumping during incineration may become somewhat troublesome after the tube has been used a few times.



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CHAPTER V

OTHER TESTS FOR INVESTIGATING RENAL FUNCTION

THOUGH blood urea estimation gives valuable information in the more or less advanced grades of nephritis already mentioned, there remains a large number of cases in which the condition has not developed to an extreme degree, but in which the kidneys, though efficient enough to prevent an accumulation of urea in the blood, may yet be gravely involved. Such cases are very commonly met with at the present time in men who contracted war nephritis during military service; the finding of protein and casts in the urine does not help us much, and in the great majority of these patients, experience shows that the blood urea is normal. In endeavouring to ascertain the condition in such subjects, various tests have been employed, but many of them are of doubtful value, and some of them have been already discarded. At one time or another I have tried practically every test that has been suggested, and have now come to the conclusion that for ordinary routine work the two following simple tests will often give as much information as can be obtained by any methods at our disposal. These tests are :—

(1) The " urea concentration " test.

(2) The diastatic test.

Besides these the other commonly employed tests at the present time are :—

(3) Phenol-sulphone-phthalein and other dyes.

(4) Ambard's coefficient of urea excretion.

(5) Urea concentration factor.

(6) Chloride concentration test (already discussed in Chapter I.).

These tests are described below.

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The Urea Concentration Test.

This test was introduced a few years ago by MacLean and de Wesselow, and has given very good results. It is carried out as follows: The patient is asked to empty the bladder, and immediately afterwards he receives by mouth 15 grm. urea dissolved in about 100 c.c. of water. The bladder is emptied one hour and two hours after the urea has been given and the specimens of urine examined for urea content. Thus if urea is given at 10 a.m. a specimen of urine is obtained at 11 a.m. and at 12 a.m. If either specimen gives a percentage of urea above 2, the kidneys are held to be fairly efficient; the higher the concentration the more effective is the renal function. The reason why two specimens are taken is, that in certain patients the urea given by mouth may produce a diuresis which tends to dilute the urine passed during the first hour. In this case the second hour's specimen should be examined. Indeed, in routine work it is generally best to discard the first specimen altogether, and to rely on the result obtained from the second specimen. Not more than about 120 c.c. urine should be passed in the second hour. Occasionally, if there is much available fluid in the patient's system, it may be necessary to take a specimen after three hours, or even to repeat the test, but this is seldom necessary. In patients with marked diuresis this must be allowed for in estimating the renal function.

This test possesses the advantage that it can be carried out by anybody; it requires no manipulative skill whatever, since all that is necessary is to estimate the urea in the urine by any of the modifications of the ordinary hypobromite method. Like every other test, it has its drawbacks, but, as the result of using it in over 10,000 patients suffering from various grades of nephritis, it may be safely said that it is exceedingly useful as a simple means of ascertaining the state of the kidneys.

That it has the advantage of indicating lesions of a much slighter degree than are detected by estimation of blood

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urea is obvious from the results of experimental work. In a large number of cases of acute nephritis in which recovery was slow, and the blood urea was considerably raised, parallel estimations of blood urea and urea concentration power were carried out. It was found that long after the blood urea had gone back to normal, the urea concentration test gave evidence of still defective kidneys. It was, of course, impossible to imagine that the kidneys had quite recovered when the blood urea became normal, and there is little doubt that the urea concentration test will detect defective kidneys in chronic disease long before the condition is sufficiently severe to produce an increase in blood urea. If the test shows a concentration of over 2·5 per cent. or so, it is quite certain that the kidneys are acting very efficiently, and this has again and again been demonstrated in cases of supposed uræmia. In each instance in which the test gave a urea percentage of 2·5 or over the supposed uræmia turned out to be something else. Of all the procedures utilised in renal investigations from the clinical side this simple one gives more information in the majority of cases than any other. The 15 grams of urea given by mouth never produce any bad effects; indeed, urea may be safely given to patients showing symptoms of uræmia. The substance possesses a somewhat unpleasant metallic taste, but this may be overcome to some extent by the addition to the draught of a small amount of tincture of orange.

Estimation of Urea.

Any method may be employed, but the apparatus used should give the volume of gas evolved. A very simple arrangement, which is really a modification of Gerrard's apparatus, is sketched here (Fig. 3).

This consists of an ordinary 50 c.c. graduated burette (A) which has a glass tap (R) fixed at its upper end. This burette is connected by rubber tubing (E) with a bottle (D), containing the urine and hypobromite solution. This solution consists of about 23 c.c. of 40 per cent. sodium

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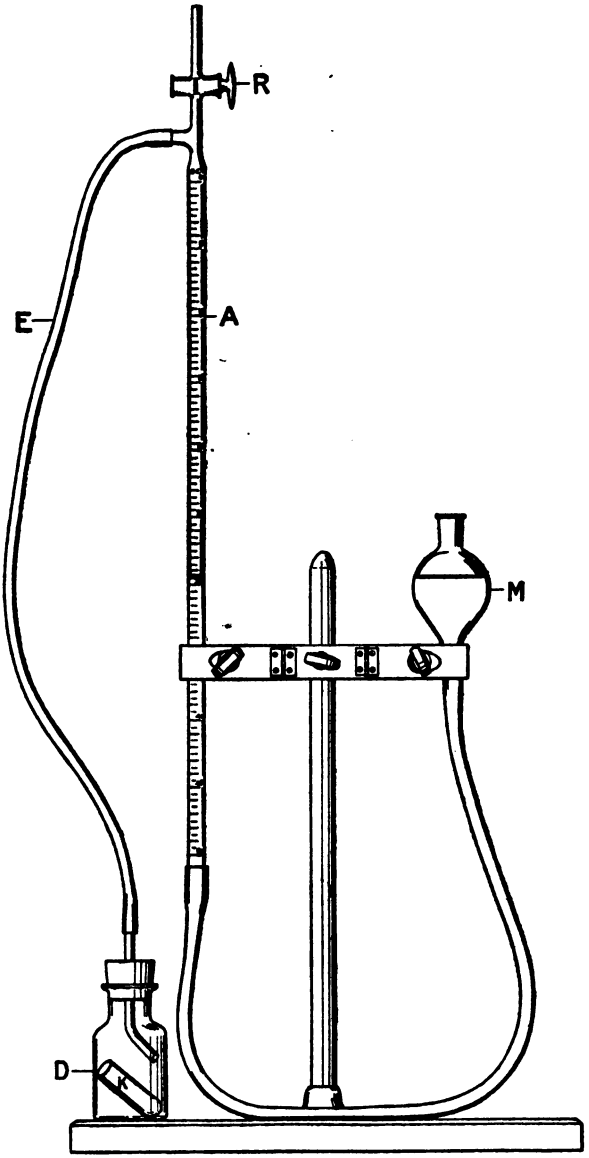

FIG. 3.—Apparatus for estimation of urea in urine.

hydroxide to which 2 c.c. of bromine are added immediately before the estimation. The lower end of the burette is

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attached by rubber tubing to a small bell-shaped vessel (M) to hold the water displaced by the evolved nitrogen. Before carrying out an experiment water is poured into the bulb M until it is about three quarters full. Care must be taken that no air bubbles remain in the rubber tube. The water of course rises in the burette until it is at the same level as the water in the bulb. In estimating the percentage of urea 4 c.c. of urine are measured into the small tube K. About 25 c.c. of sodium hypobromite are put into bottle D, and the test tube containing the urine placed inside the bottle, so that the fluids do not mix. Tap R is then opened and the rubber stopper placed tightly in bottle D. Bulb M is then raised until the level of the water in the burette is at zero. Keeping the level at zero, the tap is closed and the bulb replaced in its support. The contents of the test tube are now thoroughly mixed with the hypobromite solution, the bottle being shaken for half a minute or so. After another half-minute the bulb M is moved so as to have the level of fluid in the burette adjusted to that in the bulb. The number of cubic centimetres of gas is then read off and the urea percentage calculated from the table on p. 57. This equivalent has been worked out by estimating the amounts of urea obtained from various specimens of urine by the very accurate urease method, and comparing these with the results by hypobromite.

The only difficulty connected with the test is the liability to diuresis in some cases. It is important to note, however, that the passage of very considerable amounts of fluid does not necessarily mean a low concentration of urea in the urine, for a quite healthy kidney generally succeeds in concentrating to 2 per cent. or over, even when considerable amounts of fluid have been taken beforehand. The mental condition of the patient seems to play a part sometimes, for in some cases, it was noticed that very nervous persons tended to have a diuresis. On the whole, there is very little trouble in the use of the test.

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TABLE 3.

Table showing the Percentage of Urea equivalent to Cubic Centimetres of Nitrogen evolved.

(4 c.c. urine + 25 c.c. hypobromite solution used.)

Nitrogen c.c.	Urea per cent.	Nitrogen c.c.	Urea per cent.	Nitrogen c.c.	Urea per cent.	Nitrogen c.c.	Urea per cent.
8·0	0·5	22·4	1·40	36·8	2·30	51·2	3·20
8·8	0·55	23·2	1·45	37·6	2·35	52·0	3·25
9·6	0·60	24·0	1·50	38·4	2·40	52·8	3·30
10·4	0·65	24·8	1·55	39·2	2·45	53·6	3·35
11·2	0·72	25·6	1·60	40·0	2·50	54·4	3·40
12·0	0·75	26·4	1·65	40·8	2·55	55·2	3·45
12·8	0·80	27·2	1·70	41·6	2·60	56·0	3·50
13·6	0·85	28·0	1·75	42·4	2·65	56·8	3·55
14·4	0·90	28·8	1·80	43·2	2·70	57·6	3·60
15·2	0·95	29·6	1·85	44·0	2·75	58·4	3·65
16·0	1·00	30·4	1·90	44·8	2·80	59·2	3·70
16·8	1·05	31·2	1·95	45·6	2·85	60·0	3·75
17·6	1·10	32·0	2·00	46·4	2·90	60·8	3·80
18·4	1·15	32·8	2·05	47·2	2·95	61·6	3·85
19·2	1·20	33·6	2·10	48·0	3·00	62·4	3·90
20·0	1·25	34·4	2·15	48·8	3·05	63·2	3·95
20·8	1·30	35·2	2·20	49·6	3·10	64·0	4·00
21·6	1·35	36·0	2·25	50·4	3·15		

SOME RESULTS OF UREA TEST IN NORMAL AND PATHOLOGICAL PATIENTS.

The tables on p. 58 give some figures showing the concentration of urea in the urine in normal and pathological cases. In each instance 15 grm. of urea were given by mouth, and the urea in the second hour's specimen estimated.

Table 4 shows the results obtained with normal subjects of different ages; it will be noted that young people tend to concentrate urea somewhat better than older subjects.

Table 5 gives some figures obtained in cases of well-marked nephritis. In many of them the blood urea was increased, while in others it was within normal limits.

Along with this test the writer always uses the diastatic test. It is easy to carry out and very helpful as a rule in conjunction with the urea test.

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TABLE 4.

Normal Subjects of Different Ages.

	Medical students (age 18 to 25).		Medical men and patients (age 25 to 45).		Hospital patients (age 45 to 65).	
No.	Concentration of urea per cent.	Urine in 2nd hour in c.c.	Concentration of urea per cent.	Urine in 2nd hour in c.c.	Concentration of urea per cent.	Urine in 2nd hour in c.c.
1	2·9	140	3·0	120	2·1	140
2	3·3	110	3·1	90	2·3	130
3	3·9	100	2·9	88	2·9	95
4	4·1	105	2·7	127	3·3	80
5	4·1	115	4·0	74	3·6	85
6	2·4	90	3·2	90	2·2	94
7	2·1	130	2·3	130	2·8	120
8	3·5	80	3·4	48	3·0	120
9	3·9	110	2·6	100	2·2	125
10	3·1	52	2·9	95	2·1	140

TABLE 5.

Patients suffering from Nephritis.

No.	Concentration of urea in urine per cent.	Amount urine passed in 2nd hour in c.c.	Blood urea in mgrs. per 100 c.c.
1	1·5	100	30
2	1·7	58	60
3	0·95	195	120
4	1·2	65	90
5	1·1	80	75
6	1·9	140	20
7	0·8	70	120
8	1·1	115	—
9	1·0	110	24
10	1·3	45	28

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The Diastatic Test.

This test depends on the presence of diastase (the ferment which changes starch into sugar) in the urine. This diastase is obtained from the blood, which in turn gets it from the pancreas. Normally, blood contains a definite amount of diastase, and when the kidneys are efficient a fairly constant amount is excreted daily in the urine. When the kidneys are defective, the amount is lower, the total quantity eliminated depending on the degree of deficient renal action. The diastatic activity of any specimen of urine is estimated in terms of the amount of starch which a definite volume of the urine will change in a given time, the disappearance of the starch being indicated by the failure of the mixture of starch and urine to give a blue colour with iodine. On the whole, this test gives good results when it is possible to get a sample of the 24 hours' urine, but it is not so accurate with single specimens of urine passed at different times of the day.

A high diastatic value is, in the majority of cases, an indication of efficient renal action, but the test should never be relied on alone, for occasionally one sees patients in whom the kidneys are markedly involved, and yet the diastatic test is normal or above normal. In two patients under my care, it gave a value of 20 on each occasion on which the test was done, and yet both patients died of uræmia within a fortnight of entering hospital. These anomalous results are difficult to explain, and do not appear to depend to any extent on changes in the amount of diastase in the blood; at least, this was so in a few cases investigated by me.

Method of carrying out Diastatic Test.

The following solutions are required:—

(1) A 0·1 per cent. solution of "Soluble Starch." This is prepared by heating 0·1 grm. of soluble starch in a small amount of boiling water, cooling, and making up the total volume to 100 c.c.

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(2) A 0·9 per cent. Sodium Chloride solution. For this solution the sodium chloride may be weighed out roughly.

(3) A solution of Iodine about one-tenth normal.

In carrying out the test, six test tubes are taken and numbered with a glass pencil. The amounts of urine and normal saline shown in the table are then added to each tube, saline being used to make the total volume up to 1 c.c. For adding these fluids 1 c.c. pipettes graduated in hundredths are most suitable. The unit values corresponding to each tube are given in the last column.

TABLE 6.

No.	Urine, c.c.	Normal saline, c.c.	Unit value corresponding to each tube.
1	1·0	—	2·0
2	0·6	0·4	3·3
3	0·4	0·6	5·0
4	0·3	0·7	6·6
5	0·2	0·8	10·0
6	0·1	0·9	20·0

When the tubes are ready, 2 c.c. starch solution are added to each; this is most conveniently done from a burette. The mixture is quickly shaken, and the tubes put into an incubator or hot water bath at 37° C. for exactly 30 minutes. The tubes are then removed and filled to within an inch of the top with cold water. This stops the ferment action. One drop of iodine is now added to each tube, beginning at No. 6. On shaking, it will often be found that the last two tubes (Nos. 5 and 6) are still blue, but that No. 3 is colourless or has only a faint pink tint. If so, No. 3 tube contains just sufficient urine to change the 2 c.c. of starch in half an hour. The empirical unit denoting the change is obtained by dividing 2 (the amount of starch solution taken in cubic centimetres)

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by the amount of urine in the tube in which all the starch is changed. For No. 3 tube this would be $\frac{2}{0{\cdot}3} = 6{\cdot}6$ units. In the case of tubes containing fairly large amounts of urine, it may be necessary to add more than 1 drop of iodine, since urine itself may take up some iodine. On this account the first drop of iodine added may show no blue colour even when unchanged starch is present. On the addition of another drop, however, the blue colour will appear. Naturally, a greater number of tubes may be employed, but for practical purposes six or even less are sufficient.

The majority of normal urines show a diastatic activity of from 10 to 20 units. In some patients with quite healthy kidneys the value may be as low as 6, or perhaps occasionally somewhat lower. Values below 6, however, are suspicious. Higher values than 20 are sometimes met with in normal subjects, but the value for healthy individuals may be taken roughly as from 6 to 20 units. The urine of patients suffering from advanced renal disease may be considerably under 1, and the lower the value the more grave the condition. The test is very useful, though somewhat erratic in a few cases. Taking everything into consideration, one can say that it is of considerable value in estimating renal efficiency, especially when used in conjunction with other tests. A number of the results obtained with this test in normal and nephritic patients are recorded in Chapter VII.

Ambard's Coefficient of Urea Excretion.

As the result of extensive experimental work, Ambard concluded that the concentration of urea in the urine was closely related to the amount present in the blood. On this basis he formulated his well-known laws of urea excretion:—

(1) When the concentration of urea in the urine is constant, the quantity of urea excreted in the urine varies proportionately to the square of concentration of urea in the blood.

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(2) When the concentration of urea in the blood remains constant, the quantity excreted in the urine varies inversely as the square root of the concentration in the urine.

From these laws Ambard evolved a constant for the elimination of urea by the human kidney according to the following formula :—

$$K = \frac{Ur}{\sqrt{D \times \frac{70}{W} \times \sqrt{\frac{C}{25}}}},$$

where Ur = Grams of urea per litre of blood;
D = Grams of urea excreted in 24 hours;
W = Weight in kilos;
C = Grams of urea per litre of urine;
70 = Standard body weight in kilos;
25 = Standard concentration of urea in grams per litre of urine.

In normal healthy subjects Ambard found that this constant K varied from 0·06 to 0·07. In patients with renal inefficiency it is claimed that the renal defect is indicated by a rise in K.

This imposing formula has been modified in America by F. C. McLean, who makes use of the expression

$$K = \frac{Ur}{\sqrt{\frac{D}{W} \times \sqrt{C.}}}$$

Using this formula, K values in normal individuals vary from 0·20 to 0·36.

The first suggestion conveyed by these expressions is that here we have a method of ascertaining with mathematical exactness the condition of the renal function. All the various factors are easily obtained, and it might be thought that different grades of renal inefficiency would be indicated by proportional changes in K. Even on theoretical grounds, however, a critical examination of the formulæ leaves some doubt as to their value in estimating kidney function. Thus, in either of these formulæ, it is quite clear that the simplest way to influence K is to change

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the value of the numerator. In other words, K will be raised when the blood urea is raised. On the other hand, fairly large changes in the figures making up the denominator part, produce but little effect, since they become active only in terms of their square or fourth root. Thus, in chronic nephritis, concentration of urea C is an important factor, as it tends to decrease in bad cases, but in the formula comparatively large variations in C produce only a negligible effect on K, and any actual change found in practice is not sufficient to influence the result. Again, D (grams of urea excreted in 24 hours) varies but little, if at all, even in very bad cases of chronic nephritis, as has been already shown. Theoretically, therefore, it would seem as if the method could be of little value except in cases where the blood urea is above normal, and in such cases it is obviously unnecessary to work out a complicated mathematical problem, since the simple estimation of blood urea alone supplies us with as much information as the formula will give.

These theoretical considerations are in my experience entirely borne out by practical results, for, in the examination of a long series of cases, no information could be obtained by means of this method, except in cases where the blood urea was raised, and here, as already stated, it was quite superfluous. In short, for practical clinical purposes these elaborate expressions are, in my opinion, of little or no value.

Urea Concentration Factor.

Though mathematical calculations such as the above do not afford us much help in clinical work, a good deal of useful information may be obtained by comparing the concentration of the urea of the blood at a given time with that in the urine secreted over a short period. Normal kidneys are capable of concentrating urea to 70 times or more its concentration in the blood. Thus, if a sample of blood is found to contain 20 mgrs. urea per 100 c.c., and a sample of urine collected during the same hour as the blood

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was drawn shows a concentration of 1,400 mgrs. per 100 c.c. (1·4 per cent.), it is obvious that the blood urea as it appears in the urine has been concentrated 70 times. This number, represented by

$$\frac{\text{Milligrams urea per 100 c.c. urine}}{\text{Milligrams urea per 100 c.c. blood,}}$$

may be low in nephritic cases, and when it gets below 10 the condition is grave. To avoid confusion with the "urea concentration test," this number might be referred to as the "urea concentration factor."

Various Dye Tests.

Many dyes have been used from time to time in an endeavour to test the renal function. A certain amount of the particular dye employed is given by mouth or injected into the body, and the amount excreted in the urine in a given time ascertained. In a few cases, the time taken for the drug to appear in the urine is estimated on the principle that a delayed excretion indicates a diseased kidney. Of the many dyes used, such as methylene blue, indigo carmine, etc., several have been discarded. The most popular dye in use at present is phenol-sulphone-phthalein, or "phenol red."

Phenol-sulphone-phthalein Test.

This test for renal function was introduced into clinical work by Rowntree and Geraghty in America. The dye is non-toxic to the body and is completely and rapidly eliminated without chemical change by healthy kidneys, but more slowly, and occasionally not at all, when these organs are diseased. It is generally used as an injection, for which it is very suitable, as no local irritation ensues. One of its chief merits, from the point of view of a renal test, lies in the brilliant red colour which it produces in alkaline solution, thus permitting its accurate estimation by the usual colorimetric method. The solution employed is prepared by taking 0·6 grm. of phenol-sulphone-phthalein and 0·84 c.c. of 2N NaOH, and making the whole up to 100 c.c. by the addition of 0·75 per cent. sodium chloride

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solution. To this a few additional drops of 2N NaOH are added until the solution assumes a bright Bordeaux red colour. This solution is non-irritating, and is put up commercially in small ampoules of slightly over 1 c.c. capacity; each cubic centimetre of the solution contains exactly 6 mgrs. of the dye.

Details of Procedure.

In order to ensure free secretion of urine, the patient to be investigated is given a glass of water half an hour beforehand. An ampoule containing the dye is now opened and the contents drawn into a small syringe, so graduated that it will deliver exactly 1 c.c. The bladder is emptied and 1 c.c. of the solution injected fairly deeply into the lumbar region. Occasionally, the injection is made intravenously, and sometimes subcutaneously, but the muscles of the lumbar region are generally chosen. Ten minutes are allowed for the beginning of the excretion of the dye. One hour after this the bladder is emptied and the specimen kept for analysis. This is repeated after another hour. For instance, if the injection was given at ten minutes to twelve, the first specimen of urine would be collected at one, and the next at two o'clock. The specimens are kept in separate bottles, numbered 1 and 2. In surgical cases it may be necessary to arrange for the removal of the urine by means of a catheter. The amount of urine passed should in each case be measured. When both specimens are obtained, the next procedure is to ascertain the amount of the dye excreted in each specimen. This is done as follows:—

To bottle No. 1 add 10 c.c. of 10 per cent. sodium hydroxide solution, and dilute to a given volume with tap water, so that it may be compared with a standard. The exact dilution required depends on the depth of colour produced by the addition of alkali, *i.e.*, on the amount of dye excreted. If there is very little colour, dilute to 100 c.c. or 200 c.c.; if more colour, to 500 c.c., or in case of very good excretion to 1,000 c.c. This dilution must be

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done accurately, and the resulting solution thoroughly mixed. The most suitable dilution is very soon gauged after a little practice of the method. The ideal is to have a dilution not differing materially from the standard in depth of colour. The standard is prepared by introducing 1 c.c. of phenol-sulphone-phthalein solution from another ampoule into a graduated 1,000 c.c. flask containing 10 c.c. of 10 per cent. sodium hydroxide, and making up the total volume to exactly 1,000 c.c. This solution keeps for some months. The estimation is made preferably by a Duboscq colorimeter. Into one cup, some of the standard solution is introduced, and the standard set to 10 mm. In the other cup the solution to be tested (from urine 1) is placed, and the depth adjusted until the two fields of the instrument show the same depth of colour. Since the concentration of the standard is known, the concentration of the diluted urine solution is easily ascertained. Thus, if the unknown solution in a column of 20 mm. matches the standard set at 10 mm., then the strength of the unknown is $\frac{10}{20}$, or half that of the standard. From this an estimation of the total amount of dye excreted is made, and hence the percentage in the urine of the total amount injected is known. Exactly the same procedure is carried out with the specimen of urine passed during the second hour. In a normal case one generally obtains figures of the order indicated :—

First hour	=	40—60 per cent.
Second hour	=	20—25 „
Total	=	60—85 „

If the kidneys are healthy, from 60 to 85 per cent. of the dye is usually excreted in the two hours, and perhaps, in a normal case, at least 40 per cent. should be excreted in the first hour. When the kidneys are moderately diseased about 50 per cent. of the dye is excreted in two hours, but when the lesion is serious very little, or none at all, may appear. When excretion is found to be continually below 40 per cent. in two hours the kidneys are generally badly damaged, and in such cases the blood

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urea will usually be found to be considerably above normal. In uræmia and conditions bordering on this state it is not uncommon to find a total inability to excrete the dye.

In conjunction with other methods, this test is undoubtedly of much value, but it is rather technical, and though apparently simple, is really somewhat difficult to carry out with success. The estimation of the amount of dye excreted requires a colorimeter, and though certain investigators consider that the results are accurate when they estimate the excreted dye directly by comparison with a standard in a test tube, it is certain that these results are usually very wide indeed of the mark. When carrying out the test in this way errors amounting to 20 per cent. and 30 per cent. are possible. One of the chief difficulties, however, consists in the fact that the standard is made up with water, whereas the solution to be compared contains urine, which in itself is always coloured with pigment. These pigments influence the readings of the colorimeter, and sometimes make it impossible to get a satisfactory result. Even when the standard is made up with a certain amount of urine obtained from the patient before the injection of the dye, the result is not always much better, for the urine excreted before the test may be quite different in colour from that excreted during the test. The presence of blood, even in small amounts, renders the test almost useless.

In acute nephritis the excretion is generally low, but sometimes an increased excretion is found, while occasionally, in chronic nephritis of an advanced degree, normal excretion is seen. The test is undoubtedly very useful, but it should be used with other tests. In my hands, the results have not been altogether satisfactory, but perhaps this is too much to ask from any test. One of its main drawbacks, as a practical clinical test for every-day use, is the necessity for employing a colorimeter.

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CHAPTER VI

THE RELATION OF NEPHRITIS TO BLOOD PRESSURE AND CARDIO-VASCULAR CHANGES

SPEAKING very broadly, it may be taken for granted that, in chronic renal disease, the more serious the renal damage the higher the blood pressure and the greater the cardio-vascular involvement. This is, however, by no means always the case, and it is not uncommon to have badly damaged kidneys without any appreciable increase in blood pressure. Much more frequent perhaps is the type of case where the patient shows a decidedly high blood pressure with slight albuminuria and definite arterial changes. Such cases are generally diagnosed as primary interstitial nephritis with secondary cardio-vascular changes. In many such patients it is found that the kidneys are comparatively unaffected, and I have on several occasions examined patients who were supposed to be suffering from uræmia and in whom the kidneys proved to be quite efficient. As already stated, it is certain that no patient can be suffering from uræmia if, after receiving 15 grm. of urea, he passes a urine containing 2·5 per cent. or over of urea. Indeed, it is almost certain that a urea concentration considerably lower than this precludes uræmia. Sometimes, however, these patients on being tested pass specimens of urine containing from 3·5 to 4 per cent. urea, while the other tests described also indicate that the kidneys are efficient. This is an important observation, for the prognosis in many cases of raised blood pressure is dependent to a great extent on renal condition. Arterio-sclerosis in a patient with comparatively active kidneys is often not so hopeless as it would be if the kidneys were badly involved, and it is now generally admitted by those who have carefully studied the subject that arterio-sclerosis may sometimes be present without the

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kidneys being much, if at all, involved. Clinical symptoms suggesting uræmia are by no means uncommon in patients with raised blood pressure. For instance, patients may complain of severe headache and vertigo with various obscure pains in the chest and abdomen; attacks of extreme and uncontrollable vomiting may be present, and even convulsions may ensue. On examination a trace of protein is probably found, and superficially the whole picture resembles uræmia. Clinically, however, there are often a few points in which the condition seems to differ from true uræmia. The tongue may be clean, and the general look of the patient is not quite what we are accustomed to see in advanced uræmia, where the tongue is generally foul and the patient more or less lethargic. In such cases examination of the renal function by the tests described will often show that the kidneys are quite efficient, and that the condition, however much it resembles uræmia superficially, cannot be due to defective kidneys. The following notes of cases which have been under my care serve to illustrate these points :—

Case I.—Patient, aged 50, had done military service in France for two years, during which time he apparently enjoyed good health. Shortly after demobilisation he was found in the street suffering from convulsions, and was taken to hospital, where the condition was diagnosed as uræmia. While in hospital he had several fits, and about 20 ounces of blood were removed. This relieved him, and the fits stopped. On admission his systolic blood pressure was over 300 mm. of mercury; in fact, it was too high to be measured by the instrument available. The urine contained protein and casts. The blood pressure after a few days remained about 240. The heart was enlarged with a thudding first sound and a sharp accentuated second sound, while the radial arteries were definitely thickened. Examination of the renal function gave the following results :

Blood urea = 20 mgrs. per 100 c.c.

Urea concentration test = 3·2 per cent. urea.

Diastatic reaction = 20.

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Protein present in fair amount in urine; some hyaline and a few hyalo-granular casts also present.

These results proved beyond dispute that the condition could not be uræmia, for the kidneys showed no sign whatever of defective action. After a few weeks the patient left hospital feeling very much better, though, of course, his high blood pressure still persisted. This was obviously a case of arterio-sclerosis with convulsions, but, in spite of the cardio-vascular changes, the kidneys had escaped any serious damage.

Case II.—Patient, a business man, aged 41, had uncontrollable attacks of vomiting and vertigo. Urine contained a small amount of protein and a few hyaline and epithelial casts. Systolic blood pressure varied from 190 to 210 mm. of mercury, but the heart was only very slightly enlarged, and no definite changes in the peripheral arteries could be made out. There were occasionally slight twitchings of the facial muscles and pain in the chest and abdomen. He also complained of temporary attacks of defective vision, but, on examination, no eye changes of any kind were found. The case was diagnosed as uræmia, a condition which the clinical symptoms certainly seemed to suggest. On examination of the renal system, however, this diagnosis was definitely excluded, as the following figures show:—

Blood urea = 30 mgrs. per 100 c.c.

Specimen of urine passed after blood withdrawn = 1·9 per cent. urea.

Concentrating power of kidney for urea (urea concentration factor) = 63.

Urea concentration test = 3·4 per cent. urea.

Diastatic test = 25.

Here, again, the kidneys were quite efficient, and the presence of some protein and a few epithelial and hyaline casts was of comparatively little importance. The patient was sent for a holiday and given directions as to food and general *régime*. He has not had another attack during the last nine months.

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Several other cases of a similar kind have come under my observation. In cases of this nature the presence of protein and of a few casts in the urine generally clinches the diagnosis in favour of uræmia or chronic nephritis, but this may, of course, be entirely misleading. In every patient with the symptoms described it is necessary to investigate the renal efficiency by the usual tests. When this is done, a fair number of patients who were supposed to be the subjects of chronic nephritis, and whose symptoms suggested uræmia, will be found to have quite efficient kidneys. Indeed, cases of alleged chronic interstitial nephritis have been described in which renal tests gave good results quite incompatible with the supposed condition of the kidneys, and these anomalous results have been brought forward as an indication that renal tests are not always reliable. In such cases it is the diagnosis that is at fault, and not the tests. In many cases it may be quite impossible to ascertain by clinical means to what extent a patient's symptoms are due to cardiac or renal involvement, but this is generally quite easily discovered by renal tests, for, though blood urea may be high in cardiac cases, the urea concentration test will also be high; when the high blood urea is due to renal defect the urea concentration test will be low. Some observers recommend the indirect method of giving digitalis in such cases on the general assumption that cardiac patients will respond to this drug, while renal ones will not. Personally I have seldom experienced any difficulty in arriving at a definite diagnosis in this class of case by means of the various renal tests. Here perhaps the urea concentration test and the urea concentration factor often give most help. The diastatic test is also of great value.

In well-established renal disease the blood pressure in many cases bears some general relationship to the gravity of the disease, but there are many exceptions in individual cases, and it is just as true that extensive renal disease may exist with little or no increase in blood pressure

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as it is that arterio-sclerosis may be present without much renal involvement. The following figures, taken from a series of patients examined for the Ministry of Pensions, show that blood pressure and renal condition do not always run parallel :—

TABLE 7.

No.	Blood pressure.	Urea test.	Diastatic test.	Protein.	Casts.	General condition of kidney.
1	178	2·5	10	Fair amount .	Hyaline and epithelial.	Good.
2	180	1·2	1	Small amount	Few epithelial	Bad.
3	165	1·1	5	Small amount	Hyaline .	Bad.
4	160	1·8	6	Trace . .	*Nil* . .	Fairly good.
5	180	2·7	20	Trace . .	*Nil* . .	Good.
6	175	2·4	15	Trace . .	Few epithelial	Good.
7	164	2·0	6	Large amount	Hyaline and epithelial.	Fairly good.
8	180	1·9	1	Trace . .	Few granular	Fair.
9	170	2·6	15	Large amount	Hyaline .	Good.
10	165	2·5	10	Trace . .	*Nil* . .	Good.
11	205	1·3	4	Faint trace .	Hyaline and epithelial.	Bad.
12	172	1·2	2	Faint trace .	Epithelial .	Bad.
13	170	2·6	10	Faint trace .	Epithelial .	Good.
14	170	2·7	20	Trace . .	Hyaline and granular.	Good.
15	188	2·4	15	Trace . .	Hyaline and few epithelial.	Good.

In this connection some results communicated by Professor Boyd, of Edinburgh, to the meeting of the British Medical Association, 1921, are very interesting. This observer came to the conclusion that blood pressure furnishes no evidence as to the state of the renal function, and in support of this contention furnished a table, from which the following figures are extracted. Here the amount of non-protein nitrogen in the blood is taken as

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an index of kidney efficiency and compared with the systolic blood pressure.

TABLE 8.

Case.	Disease.	Non-protein nitrogen of blood in mgrs. per 100 cc.	Systolic blood pressure.
1	Acute nephritis	46	134
2	Chronic nephritis	41	220
3	Nephritis (uræmia)	74	140
4	Subacute nephritis	59	122
5	Chronic diffused nephritis . .	53	160
6	Chronic nephritis (cerebral hæmorrhage).	80	170
7	Subacute nephritis	98	172
8	Arterio-sclerotic kidneys (cerebral hæmorrhage).	52	170
9	Chronic nephritis	60	218
10	Chronic nephritis	54	180
11	Chronic nephritis	220	123
12	Chronic nephritis	160	88
13	Subacute nephritis, endocarditis .	123	130
14	Chronic nephritis	139	192
15	Chronic nephritis	190	175
16	Chronic nephritis	88	160
17	Subacute nephritis	59	95
18	Chronic nephritis	162	190
19	Chronic nephritis	66	210
20	Chronic nephritis	53	129

The question of blood pressure in acute nephritis has been already fully discussed in Chapter II.

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CHAPTER VII

THE EXAMINATION OF PATIENTS FOR RENAL EFFICIENCY, WITH NOTES OF CASES

In examining a patient for renal efficiency the exact procedure adopted must depend on circumstances. When the necessary laboratory accommodation is available, all the tests mentioned below might with advantage be carried through, but very often, especially in the case of a general practitioner, facilities for any but the most simple methods are wanting. Estimation of blood urea is certainly important in many cases, and if possible it should be done whenever the clinical condition and history of the patient suggest that the renal functions are considerably impaired. On the other hand, it is quite possible to obtain a very great deal of information by means of the simpler tests, and in the majority of cases the busy medical man ought to be able to determine for himself the condition of his patient. Naturally it is best to examine the patient as thoroughly as possible by various methods, but when this is difficult or impossible much can be learned from such simple procedures as the urea concentration test alone. The simpler the tests the more useful they are, but unfortunately, from the very nature of renal action, many of these tests for renal function are necessarily somewhat complicated, and require time and care if satisfactory results are to be obtained. The interpretation of all these tests must, of course, be made with care, but after a little practice in their use no difficulty should be experienced.

After the War I was asked by the Ministry of Pensions to evolve a scheme for the examination of persons suffering from the effects of war nephritis, for it soon became obvious that the ordinary methods of examination of the urine for protein and casts did not give much information. Certain patients whose condition from this point of

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view apparently entitled them to a large pension were known to be able to complete a full day's hard manual labour without inconvenience, while in other cases, though the patient looked well and the urine contained only traces of protein, he broke down after slight exertion and was really unfit for work. A scheme of examination suitable for the purpose required was somewhat difficult to suggest, for certain conditions had to be fulfilled. For instance, the patient was available only for a short time, and a great number of patients had to be tested per day. Again, the smallest possible interference with the patient was indicated, and on this basis alone the use of such tests as phenol red, in which injection was necessary, had to be abandoned. For this and other reasons blood urea examinations also could not be adopted as a general procedure. After a good deal of experimental work the following scheme was evolved, and is now in use all over the country in the clinics of the Ministry of Pensions. The scheme has given good results, and being simple and easy to carry out, furnishes, in my opinion, all the information necessary in the great majority of cases of nephritis. In all renal patients it is, of course, very important to examine carefully the condition of the cardio-vascular system as well as the kidneys. This scheme is as follows :—

SCHEME FOR EXAMINATION OF RENAL PATIENTS.

(A) Examination of specimen of urine passed by patient for [1]—	(1) Protein (p. 77); (2) Casts or other abnormal elements, such as pus, blood and spermatozoa (p. 78); (3) Diastatic test (p. 59). (Normal average 6 to 20.)
(B) Urea concentration test.	Immediately on passing water patient receives 15 grm. urea; he remains for two hours, and empties his bladder each hour, as already described (p. 53). Specimens passed are measured and kept for urea estimation.

[1] It is best to use a 24 hours' specimen if this can be obtained.

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(C) Note presence or absence of œdema.

(D) Cardio-vascular condition (p. 79).
- (1) Blood pressure.
- (2) Apex beat position and nature of cardiac sounds.
- (3) Condition of arteries.

(E) General condition of patient.

The scheme is easy to carry out, and has the advantage that large numbers of men can be examined at the same time. In one clinic as many as 50 patients have undergone the examination in one day, and 30 to 40 are looked upon as an ordinary number. During the last two years considerably more than 10,000 examinations have been carried out under my personal supervision, so that I am now in a position to testify definitely to the value of the procedure. This scheme could in its entirety be carried out by any practitioner on private patients; the only test requiring any special apparatus is the estimation of diastatic activity, and that necessitates an incubator or hot water bath maintained at a constant temperature of 37° C. Anybody possessing an incubator can easily perform the test, as the procedure is exceedingly simple. When facilities for this test are available it ought to be used with the others, but in many cases experience shows that it can be omitted. Generally it merely confirms the results of the urea concentration test. Excluding the diastatic test, therefore, the above scheme is about the extreme of simplicity to which any satisfactory renal examination can be reduced. Despite its simplicity, however, it gives most useful results, and there is no reason why it should not be adopted by every practitioner in suspected cases of renal disease.

On the other hand, when the necessary facilities are available the following more elaborate scheme for examination is suggested:—

(1) Examination of urine for protein and casts.
(2) Estimation of blood urea or non-protein nitrogen.
(3) Urea concentration factor.

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(4) Urea concentration test.
(5) Diastatic test.
(6) Presence or absence of œdema.
(7) Apex beat position and nature of cardiac sounds.
(8) Blood pressure.
(9) Condition of arteries.
(10) General condition of patient.

In the carrying out of certain of these procedures, the following points, bearing on the examination of urine and casts and on the method of estimating blood pressure, will now be considered :—

EXAMINATION OF URINE FOR PROTEIN.

For the detection of albuminuria the methods chiefly in vogue at present are (*a*) the heat coagulation test and (*b* Heller's cold nitric acid test. Both these tests are satisfactory when carried out with care, but under certain conditions they are not very convenient. Of all protein reagents by far the best is salicylsulphonic acid. This substance is a white powder exceedingly soluble in water, and a saturated solution in distilled water constitutes the most perfect reagent for protein testing that we know of ; it is non-corrosive, and may be carried about in the pocket, and its method of use is so simple that any one can use it. In testing for protein, 6 drops or more of a saturated aqueous solution of this acid are added to about half an inch or so of urine in a test tube.

In the presence of a fair amount of protein a dense white precipitate immediately forms, while smaller amounts produce less dense precipitates, varying from a very definite milkiness to a faint opalescence. The test is very delicate and for practical purposes excellent. It is somewhat more sensitive than are either of the other tests mentioned, and it is difficult to understand why it is not in universal use. Any urine that does not give an opalescence or precipitate on the addition of salicylsulphonic acid is certainly free from protein. It should be noted that urines do not give the test unless the reaction of the

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mixture of salicylsulphonic acid and urine is acid, but obviously, even in alkaline urines, the addition of the reagent renders them acid; and it is only in a very few cases of exceptionally alkaline urine, such as that which results after large doses of alkali, that protein could possibly be missed. In such cases the addition of a few drops of acetic acid to the urine before adding the reagent gets over the difficulty.

EXAMINATION FOR CASTS.

Casts should be examined for with the microscope after centrifuging the urine. The only point to emphasise is the necessity for using as small a diaphragm as possible, for if this is neglected certain fine casts may be easily missed. The most suitable lens is an ordinary two-thirds objective with a No. 3 or No. 4 eyepiece. A mechanical stage is useful, especially if large numbers of patients are to be examined. If a centrifuge is not available, the urine should be left to stand for a few hours in an ordinary urine glass. In examining the deposit it is best to pipette about 0·5 c.c. of material from the bottom of the glass or test tube and to spread this in a thin layer over the greater part of a microscope slide. It is then examined with a low power. Occasionally it may be necessary to use a high power for purposes of identification of the structure of the casts, but this is seldom necessary.

Nature of Casts.

Casts are chiefly of three kinds: blood, epithelial and hyaline. Epithelial and blood casts, however, may undergo a process of degeneration, so that on examination blood or epithelial cells may be represented only by a few granules; in such casts a hyaline matrix studded with small granules, with an occasional more or less complete cell, is found. For purposes of reference these degenerated products may be termed hyalo-granular casts. These varieties include all the various kinds of casts we meet with in ordinary cases of nephritis.

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CARDIO-VASCULAR CHANGES.

Although kidney tests are essential in every case of suspected kidney disease, it is very important not to forget to examine the cardio-vascular system. This is done by the ordinary clinical methods. Since the estimation of blood pressure sometimes gives rise to difficulties, a description of the procedure now generally adopted is given here.

ESTIMATION OF BLOOD PRESSURE.

This is best carried out by means of a modified Riva-Rocci sphygmomanometer, consisting of a mercurial manometer, an armlet containing a rubber bag for compressing the upper arm and a bulb with a double valve for inflating the armlet. Attached to the inflating bulb is a valve worked by a screw, by which the pressure in the armlet can be gradually reduced. The general arrangement is shown in Fig. 4. The actual estimation may be done either by the palpatory or auscultatory method, but the latter procedure gives the best result and should always be used.

Procedure for Auscultatory Method.

The patient should be in a sitting position and generally relaxed with his arm supported on a table about the level of his heart. Care should be taken to set him at ease, since the estimation may be vitiated by nervousness and excitement on his part. The arm is now bared, and that part of the armlet containing the rubber bag is wound round the upper arm a little above the elbow; the remainder of the armlet is bandaged round the arm, the end being passed under the preceding fold. The chest piece of a binaural stethoscope is now placed over the brachial artery just above the bend of the elbow, and the pressure in the armlet increased by means of the inflating bulb. At a certain point during inflation a throb of pulsation is heard, and this throb maintains its loudness for a certain time as inflation proceeds, but soon it diminishes, and

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ceases abruptly at a point corresponding with the cessation of the pulse at the wrist. The air is then slowly allowed to escape from the armlet, the eye watching the fall of the mercury in the manometer. As soon as a little blood escapes beyond the armlet a faint but clear, sharp sound is heard in the artery, and the mercury begins to oscillate faintly with each cardiac beat. The height of the mercurial column at this point is taken as indicating the systolic pressure. As deflation proceeds the clear sound is replaced

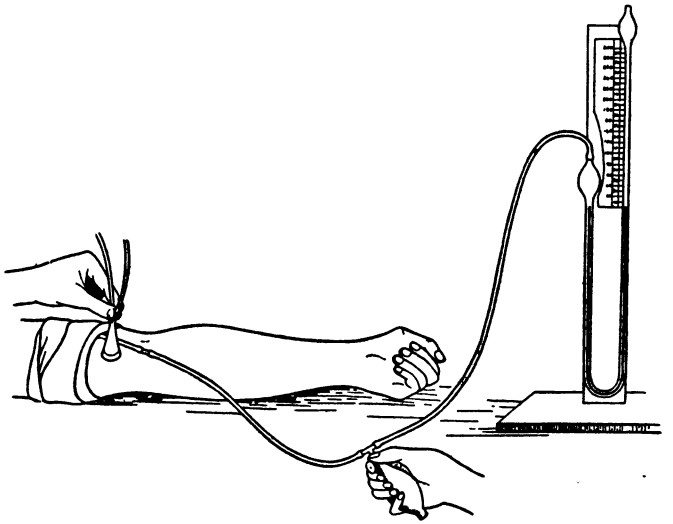

FIG. 4.—General arrangement for ascertaining blood pressure.

by a more or less decided murmur, which in turn is soon followed by a clear, distinct and usually loud sound; this sound continues till the pressure gets very low, when it ceases. Just before it ceases the sound changes its character and becomes muffled and dull. The height of the mercury at this point indicates the diastolic pressure.

It is well to remember that the auscultatory method gives an average reading 6 to 8 mm. higher than the palpatory one. Though a little more difficult to carry out, it gives very satisfactory results, and a very little practice soon enables any one to master it.

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Some Observations on Cases.

In examining patients for renal efficiency we generally deal with two chief classes of cases: (1) patients in whom a renal lesion is suspected owing to the presence of albuminuria or other symptom and (2) patients who are known to be suffering from nephritis. In the latter case we wish to ascertain to what degree the renal functions are involved. It must be repeated that no criterion as to the extent of the disease is afforded by the amount of protein found in the urine nor by the casts present. Our estimation of the gravity of the condition must rest almost entirely on the results of other tests. In many cases of albuminuria of adolescence, for instance, the clinical condition strongly suggests the presence of nephritis, and the urine may contain a fairly large amount of protein and some hyaline and even epithelial casts, yet the urea concentration test may entirely exclude nephritis.

The following are examples of such cases :—

Case I.—Patient, aged 14, was unable to do his school work, and found his games too hard. On examination by his medical attendant a fairly large amount of protein was found in the urine. He was ordered a holiday and put on a strict diet, but after a few months did not improve, the albumin, if anything, being more marked. As nephritis was suspected, a thorough examination for renal efficiency was carried out, with the results given below. A study of these results shows that the case was one of adolescent albuminuria, no evidence whatever of defective renal action being obtained.

Urine contained 1 per cent. protein with a few hyaline and one or two epithelial casts.
Blood urea = 16 mgrs. per 100 c.c.
Urea concentration factor = 72.
Urea concentration test = 3·1 per cent.
Diastatic reaction = 20.
Œdema = *Nil.*
Blood pressure = 110.

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Apex beat in fifth interspace internal to nipple line.
Arteries normal.
General condition: Weedy and anæmic.

On testing urine for globulin by means of acetic acid (p. 33) a distinct precipitate was obtained, which dissolved on the addition of excess of the acid. Examination of specimens of urine passed at different times of the day showed that the morning urine was generally free from protein. A return to normal diet on the part of the patient resulted in a great improvement in his condition. The assurance that his kidneys were healthy, no doubt, contributed to this.

Case II.—A bank clerk, aged 16, complained of feeling out of sorts, and on examination, urine was found to contain protein. Here again no evidence of renal disease could be obtained.

Urine contained protein and a few hyaline casts.
Blood urea = 20 mm. per 100 c.c.
Urea concentration factor = 80.
Urea concentration test = 2·9 per cent.
Diastatic reaction = 15.
Œdema = *Nil.*
Blood pressure = 125.
Apex beat in normal position.
General condition: Fairly good, slightly anæmic.
Acetic acid test for globulin negative.

Many more cases of this kind could be given, but the above will suffice to show the value of these various tests in cases of albuminuria. These patients are very often the cause of great anxiety both to their parents and to their doctor, and this atmosphere does not tend to help the patient. The danger of being subjected to an unnecessarily restricted diet is also an important point, and in all such cases an endeavour should be made to clear up the diagnosis. In the majority of cases this is easily done, and often patients and relatives can be reassured. In cases of subacute nephritis following an acute attack the kidneys can be examined at intervals, and in this way

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some idea of the progress of the patient ascertained. The following figures (Table 9), obtained from a patient during the acute stage of nephritis and at intervals of about six months afterwards for a year, are interesting. Patient was a labourer aged 27. After one year the tests gave normal figures.

TABLE 9.

	Acute stage.	After 6 months.	After 1 year.
Urine	Protein in large amount; blood and casts.	Protein in small amount; some casts.	Faint trace protein; very few hyaline casts.
Blood urea, mgrs. per 100 c.c. . .	200	43	31
Urea concentration factor . .	14	40	60
Urea test	—	1·9	2·6
Diastatic test . .	2	3	15
Blood pressure . .	135	140	140

Another patient suffering from acute nephritis was examined at intervals of about a fortnight for nearly four months. The improvement is well shown in Table 10.

TABLE 10.

	1st fortnight.	2nd fortnight.	3rd fortnight.	4th fortnight.	5th fortnight.	6th fortnight.	7th fortnight.
Urine	Protein and casts.	Protein and casts.	Protein and casts.	Protein less casts present.	Protein slight and casts.	Protein slight and casts.	Protein trace; few casts.
Blood urea, mgrs. per 100 c.c.	210	80	42	47	40	28	28
Diastatic value	<1	<1	3·3	4	2	10	6·6
Urea concentration test .	—	—	—	1·54	1·6	1·6	2·0

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In chronic nephritis much information can be obtained as to the extent of the renal damage. Sometimes in these cases the clinical condition is very deceptive, for it is not very unusual for patients with advanced renal disease to be fairly fit. In fact, such patients occasionally feel no ill effects, and sometimes the first indication of anything being wrong is the onset of uræmia. The following is an example of this type of case :—

Case V.—Patient aged 27, female, married when 21 years of age. During her whole life she had been quite fit, but a few days before her admission to hospital she complained of some headache with pelvic pain and discomfort. After admission headache became worse, but otherwise patient appeared to be in good health. As the urine contained a trace of protein and the cause of the headache was somewhat obscure, renal tests were carried out. The results were certainly alarming, as the figures show. The patient died in less than a fortnight of uræmia.

Urine = trace of protein, no casts found.
Blood urea = 290 mgrs. per 100 c.c.
Urea concentration factor = 3.
Urea concentration test = 0·9.
Diastatic test = 10.
Œdema = *Nil.*
Blood pressure = 145.
Apex beat in nipple line in fifth space.

Among other interesting features of this case is the high diastatic constant. As already indicated, this anomalous result is sometimes met with.

The table on next page, giving the findings in 20 patients examined for suspected nephritis, shows the general nature of the results obtained with the above tests. A study of the cases will indicate the kind of information which these tests furnish.

In giving a prognosis in the case of any patient it is most important to remember that cardio-vascular changes must be carefully considered, for even when the kidneys

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TABLE 11.

No.	Protein.	Casts.	Diastatic test.	Urea concentration test, per cent. urea.	Amount urine passed in 2nd hour in c.c.	Blood pressure systolic.	Remarks on efficiency of kidney.
1	+ + +	Numerous Ep., Hy., Gr.	2	1·2	56	168	Bad.
2	Very faint trace.	*Nil*	10	1·9	132	140	Good (slight diuresis in second hour).
3	+ + +	Ep., Hy., H. gr.	1	1·1	144	145	Bad.
4	+	Few Hy., Gr.	10	2·3	52	148	Good.
5	*Nil*	*Nil*	20	3·5	35	140	Kidneys efficient.
6	+ +	*Nil*	20	1·8	80	136	Fairly good.
7	+	Few Hy., Ep.	20	2·3	70	143	Good.
8	+	Few Hy., Ep.	15	3·5	45	145	Good.
9	+	Few Ep.	6·6	1·2	50	170	Bad.
10	+ + +	Numerous Hy., Ep.	10	2·6	40	132	Good.
11	+ + +	Few Hy., Ep.	6·6	3·1	48	128	Very good.
12	*Nil*	*Nil*	10	1·4	220	150	Good (diuresis in second hour).
13	*Nil*	*Nil*	15	3·8	40	136	Kidneys efficient
14	Trace	Few Hy., Gr.	4	1·1	82	160	Bad.
15	Trace	*Nil*	6·6	2·5	70	124	Good.
16	+ + +	Hy., Ep., Gr.	6·6	1·5	75	156	Very moderate.
17	+	Few Ep.	5	3	62	114	Good.
18	*Nil*	*Nil*	10	3·05	35	112	Kidneys efficient.
19	+ + +	Hy., Gr., Ep.	10	4	80	124	Good.
20	+ + +	Some Ep., Gr.	10	2·9	60	110	Good.

PROTEIN.
+ + + = Very large amount.
+ + = Large amount.
+ = Moderate amount.

CASTS.
Ep. = Epithelial.
Hy. = Hyaline.
H. gr. = Hyalo-granular.
Gr. = Granular.

are comparatively healthy, it must not be forgotten that an increased blood pressure accompanied by cardio-vascular changes may result in cerebral hæmorrhage or other complication. Broadly speaking, as already mentioned, the outlook in the case of a patient suffering from arterio-sclerosis is less grave when the kidneys are not materially involved, but such accidents as hæmorrhage may ensue at any moment, and this possibility must not be overlooked in giving a prognosis.

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CHAPTER VIII

THE IMPORTANCE OF ASCERTAINING THE STATE OF THE KIDNEYS IN CERTAIN SURGICAL CONDITIONS

One of the most important parts played by modern renal tests is the estimation of the renal function in patients suffering from certain genito-urinary diseases, such as enlarged prostate. In nearly every patient in whom there is long-continued obstruction to the passage of urine, the kidney becomes involved sooner or later, with the result that renal efficiency becomes seriously impaired. The exact cause of this deleterious action on the kidney is not quite clear, but in the majority of cases it is probably due simply to the effect of backward pressure; the kidney has to perform its work under quite abnormal conditions, and it is not unlikely that the defective renal function which commonly ensues is directly dependent on physical causes. In these patients the kidneys have to perform their work against pressure caused by the retained urine, and this soon results in marked inability to carry out their normal functions. When operative interference becomes necessary the results depend to a great extent on the state of the kidneys. If the usual tests show that the kidneys are markedly inefficient, anything in the nature of a major operation should be postponed, and nothing more than the treatment immediately necessary, such as a suprapubic cystostomy, should be undertaken. Even this should be done as rapidly as possible, using either a local anæsthetic or some such combination as gas and oxygen. Chloroform and ether should be avoided. In many of these cases a major operation, such as prostatectomy, can be performed at a later date with comparative safety, while a similar

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operation undertaken at an early stage would almost certainly have ended in disaster. Fortunately for the patient, the renal condition following retention of urine is essentially different from that found in chronic renal disease. In chronic nephritis the renal efficiency can never be recovered to any great extent, but the renal damage resulting from retention of urine is not necessarily of a permanent nature. On removal of the cause the kidneys generally improve and recover their functions to a great extent. A major operation performed at the stage when the kidneys are inefficient is very liable to increase this inefficiency to the point at which uræmia supervenes. An equally severe operation performed some weeks after relief of the retention by cystostomy or other means may be comparatively free from risk, since the danger of uræmia at this stage is often negligible.

In these genito-urinary cases the tests already described should be carried out, but in a general way the estimation of blood urea probably furnishes the most information. No surgical procedure necessitating a general anæsthetic should ever be carried out on a patient whose blood contains 100 mgrs. or more urea per 100 c.c. In every case known to the writer, with one solitary exception, operation undertaken when the blood urea was 100 mgrs. or over resulted in death. Even with lower amounts than this there is a distinct risk. In such cases the clinical condition of the patient, however good, is likely to prove a false guide if operation is undertaken on this alone ; much more important is the renal condition as indicated by renal tests. It is no uncommon experience for a patient with retention of urine, and a blood urea of 150 mgrs. or so, to improve as the result of drainage and careful nursing to such an extent that after a few weeks his blood urea may be normal. This improvement is well shown in the following cases :—

Patient, aged 55, suffering from retention of urine and enlarged prostate, had suprapubic cystostomy performed

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on admission to hospital. The result of drainage was very satisfactory.

	Immediately before drainage.	Three weeks after drainage.
Blood urea (milligrams per 100 c.c.)	96	40
Urea concentration factor	9	25
Urea concentration test.	1·2	1·3
Diastatic reaction.	6	10

While an operation on admission would probably have proved fatal, the prostate was removed with success later on.

In another patient, the clinical condition seemed to contra-indicate operation, but the renal tests showed that the kidneys were efficient.

Blood urea = 40 mgrs. per 100 c.c.
Urea concentration factor = 35.
Urea concentration test = 2·4.
Diastatic test = 10.

Here, in spite of the general clinical condition being unfavourable, the patient was operated on and the prostate removed. An uneventful recovery ensued.

All patients suffering from retention of urine and other genito-urinary conditions should be carefully examined for renal efficiency before any extensive surgical procedure is undertaken. When retention exists, drainage should be established by suprapubic cystostomy or other means. In the majority of such cases the blood urea will be found to be considerably reduced after a few weeks, and as a result the necessary surgical interference can often be successfully undertaken.

There is little doubt that in this sphere alone careful examination of the renal system has saved thousands of lives. Probably many obscure deaths after general surgical operation are due to unsuspected renal inefficiency.

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CHAPTER IX

SOME OBSERVATIONS ON THE DIETETIC TREATMENT OF NEPHRITIS

Acute Nephritis.

The active treatment of acute nephritis reduces itself largely to the treatment of symptoms, and with this we are not concerned here. The view, however, is widely accepted that a low protein diet is indicated in the early stages, especially in cases showing a retention of nitrogenous products. Very often this low protein diet is regulated according to the amount of protein appearing in the urine, so that in certain cases it is the practice of medical men to persist with it for long periods. Milk is usually made use of in this connection, and it is not infrequently forgotten that milk is a form of food comparatively rich in proteins. On general principles it is probably correct treatment to give low diets, especially as regards protein, during the early stages of the malady. When nitrogenous retention is a marked feature a diet in which the necessary calories are furnished by carbohydrate often does well. On the other hand the mistake should not be made of limiting the protein intake in all instances in which there is excessive albuminuria, for in certain cases often complicated by very persistent œdema the amount of protein actually passed in the urine may be so great as to constitute a serious loss, and in such cases it is worse than useless to restrict protein intake. Indeed, the best way to relieve the attendant œdema is to increase very largely the protein part of the diet. This action, as already indicated, is probably dependent on the diuretic action of the urea formed as the result of increased protein metabolism. Speaking broadly, it is bad practice to be guided

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as to the amount of protein in the diet by the extent of the albuminuria: after the early stages are over, and there is no longer evidence of an accumulation of urea in the blood, there is no advantage whatever in following the practice of cutting down the protein. Indeed, it will be found more advantageous as a general rule to give more protein in those cases in which there is very extensive albuminuria. Although it is often inferred that an increase of protein intake tends to raise the total percentage of protein in the urine, I have found very little evidence of this in the cases I have examined. In the urines of several patients investigated, little or no increase in the urinary protein could be ascertained after protein meals, and I am inclined to think that, if this alleged increase in albuminuria after ingestion of protein takes place at all, it is a much rarer phenomenon than is generally supposed.

It is a fact, however, that in certain cases of very severe albuminuria occurring as the result of pregnancy the amount of albumin in the urine may be very materially influenced by the amount of protein in the diet. This phenomenon is certainly different from that occurring in ordinary acute nephritis, and suggests that in these toxæmias of pregnancy we are dealing with a condition which, though it is accompanied by renal changes, yet differs materially from ordinary nephritis. It is not impossible that in this type of case the defect may be associated with the absorption of protein from the intestine, and that the renal changes may be secondary in their nature.

On physiological grounds it is difficult to understand why protein which, according to modern teaching, is hydrolysed in the intestine and resynthesised by the tissues from the amino-acids in the blood, should increase the protein of the urine. No doubt it is a difficult question to decide whether or not a large protein meal immediately increases the blood protein, but if it does so at all, it can only do it to a very slight extent if we accept as correct the modern ideas on protein metabolism. Indeed, so far as

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the evidence goes, it would appear that blood protein is only slowly built up, just as is the case in other tissues. The point to be noted is that protein is essentially different from such a substance as sugar, which is absorbed as such into the circulation and tends to increase directly the blood sugar concentration. Of course any morbid local condition allowing of absorption into the blood stream of undigested or partially digested protein would immediately result in marked albuminuria. Possibly in certain cases in which the albuminuria is directly influenced by the protein in the food something of this nature may actually be taking place. Further, there is no real evidence that protein does harm even in cases of acute disease where there is a tendency to nitrogenous retention, but in the present state of our knowledge it seems wise to enforce certain restrictions as regards protein-feeding in such patients. It must, however, be borne in mind that patients suffering from subacute nephritis should have a sufficient amount of food, for the detrimental effect of a poor diet retards progress.

Generally speaking, the dietetic treatment of a case of acute nephritis should consist in giving the patient a low diet with little protein during the early stages of the disease. As a rule it is customary to make use of milk at this stage, but too much milk should not be taken, as it is relatively rich in protein.

Immediately the initial acute stage is over it is a good plan to make up the necessary calories by means of carbohydrate food, or, if the disease is not severe, a fairly large amount of carbohydrate may be given from the beginning. As convalescence progresses protein may be gradually added to the diet, and in an ordinary case the patient may return to ordinary diet in from six weeks to two months or so. The amount of protein in the diet should not be influenced by the amount of protein in the urine; a much more scientific criterion is an estimation of the blood urea, and if this is normal or nearly normal, protein may be given in the usual amount. In cases with no increase in

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blood urea, but in which œdema is a marked feature, and the urine contains a very large amount of protein, it is always wise to give a large protein diet, as this tends to clear up the œdema more quickly than any other treatment. Also on common-sense grounds it is obvious that the great loss of protein by the urine in such patients should be compensated for by an increase in the protein of the diet. In cases of persistent œdema it is very often of advantage to combine a large protein diet with a very low salt intake or, if possible, to exclude salt altogether. The reason for this depends on the principle discussed in Chapter I. I have often seen cases in which œdema persisted while the patient was taking the ordinary amount of salt, but disappeared rapidly on cutting off salt. In long-continued severe cases of subacute nature, however, a so-called salt-free diet often fails to have any appreciable effect.

Chronic Parenchymatous Nephritis, or Hydræmic Type.

Apart from the question of general treatment, the dieting of patients suffering from this type of nephritis has always been perplexing and difficult. Recently, however, Epstein suggested that patients with marked œdema or ascites resulting from parenchymatous nephritis should receive a liberal protein diet. He claimed that this treatment resulted in a complete disappearance of the dropsy in many cases. This observation has now been substantiated, and it is generally admitted that an increase in protein intake is indicated in cases of parenchymatous disease in which dropsy plays a prominent part. In such cases the disappearance of the dropsy which often follows the change in diet is not accompanied by any definite beneficial change in the renal tissue. The amount of protein excreted in the urine is as large as ever, but the patient's general comfort is so greatly increased that he passes from a life of acute suffering to one of comparative ease and from being bedridden is often able to continue his work. This disappearance of the dropsy which so often results from

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an increased protein diet has been explained by Epstein on the supposition that the lowered plasma protein content is increased, and that consequently a greater osmotic pressure is exerted in the circulatory system. This increased pressure, according to Epstein, attracts fluid from the tissues to the blood stream, and this fluid is in turn thrown out by the kidneys.

That a high protein diet often results in the removal of the dropsy in these cases is certain, but the cause of this is not very easy to ascertain. While increase of plasma protein may perhaps be a factor in some cases, it is certainly not the essential one, for I have investigated a case in which exceedingly severe œdema and ascites cleared up in two months on high protein diet without any increase of the protein of the blood. Particulars of this case are given below (p. 94). Here it will be seen that the blood protein remained constant; indeed, if anything, it showed a slight tendency to decrease. This patient suffered from nephritis so pronounced as to necessitate tapping every two weeks. At each tapping from 8 to 12 pints of fluid were removed; œdema was also extreme, and for over six months the patient had been bedridden. The urine contained only the faintest trace of chloride.

After trying various drugs without the slightest effect, he was put on the high protein diet recommended by Epstein. For some little time his condition remained unchanged, but gradually during the next three months his daily output of urine rose from an average of 20 to 25 ounces to a maximum of 80 to 100 ounces. He was tapped four weeks and seven weeks after beginning the treatment, when 12 and 10 pints of fluid respectively were removed. Since his last tapping, now over three years ago, he has been free from ascites and œdema, has put on flesh and looks and feels much better. For the last two and a half years he has been able to perform his ordinary duties as a railway worker. The renal condition is, of course, not cured, for he still continues to pass from 12 to 20 grm. of protein per day, but his general physical comfort is

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increased to such an extent that life, which was formerly so trying for him, is now comparatively pleasant. After the disappearance of the œdema he was passing from 2 to 3 grm. of chlorides per day.

TABLE 12.

Details of Blood Protein and Urea in above Case.

	Protein in plasma. Per cent.	Urea in blood. Milligrams per 100 c.c.
On commencement of diet .	6·29	27
Four weeks after. . .	6·20	64
Six weeks after . . .	6·00	56
Eleven weeks after . .	—	81
Fourteen weeks after . .	5·96	63

Since the protein content of the plasma of this patient tended rather to decrease than increase, it is certain that in this instance, at any rate, Epstein's explanation does not hold. Even if we assume that an increased protein diet does really increase the plasma protein in some cases, it is difficult to understand why this should result in a disappearance of the œdema. On theoretical grounds, indeed, it might be argued that the result would be an increase in the œdema. It has been shown by various observers that the osmotic pressure exerted by the blood protein in an average individual represents about 30 mm. of mercury; in other words, the protein tends to draw water into the blood or to prevent its escape out of the blood. In the ordinary individual this osmotic pressure tends to prevent filtration of fluid through the glomerulus, and before filtration can take place a resistance equal to the pressure exerted by a column of about 30 mm. of mercury must be overcome. Dilution of the blood plasma tends rather to increase this filtration, as shown by Starling, because the osmotic pressure resisting filtration is decreased. Estimation of the plasma protein, however, in several other cases of parenchymatous nephritis did not indicate any increase as the result of protein feeding, yet

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in all these cases the dropsy disappeared. Since this disappearance was always associated with an increase in the blood urea, it seems almost certain that the increased excretion of fluid in such cases is due to the diuretic action of the urea in the blood.

Action of Urea in removing Dropsy in Parenchymatous Nephritis.

The fact that increased concentration of urea in the blood accompanies the clearing up of the œdema suggested that possibly urea itself might act in the same way. To test this, large doses of urea were given to several patients with marked ascites and œdema, with the result that in each case the dropsy gradually disappeared or became much less obvious. For this treatment to be successful, however, it must be persevered with for several weeks or even longer, if necessary. Thirty grams or more of urea may be given per day. To begin with, two doses of 15 grm. dissolved in a little water may be given every 24 hours, or in some cases even three doses. Soon the amount of urine passed increases greatly and may be double or treble the ordinary amount. In one case in which this treatment was tried the patient was absolutely waterlogged, and it would be difficult to imagine a more intense œdema and ascites than she exhibited. After a month of urea treatment she began to improve, and in three months was quite free from dropsy. She then left the hospital and stopped taking urea. In about a month she returned, suffering from both œdema and ascites, which were almost as marked as at the beginning. After a fortnight on urea this cleared up entirely. She was watched for some time and the urea gradually cut off. She is now quite free from œdema, and says she feels perfectly well. She has had no urea for over a year.

After-history of Parenchymatous Cases cured of Dropsy.

Probably the most dangerous variety of chronic kidney disease is that of parenchymatous nephritis accompanied

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by well-marked œdema and ascites. The tissues become waterlogged; and unless relief is obtained, the heart and lungs become embarrassed, and the patient dies, we might almost say, from drowning. Although the treatment mentioned above may often succeed in removing the dropsy, the general renal condition is not influenced, and the albuminuria remains as marked as ever. Though the patient is not cured, it is most important to relieve the dangerous dropsical condition, for in the cases that survive there is a tendency to pass from the stage in which œdema is one of the most distressing symptoms to one in which the symptoms represent those of chronic interstitial nephritis. When this stage is reached œdema is no longer in evidence, and the immediate danger to life is much less, so that the patient may live in comparative comfort for many years. It is thus most important to prevent the grave effects of excessive waterlogging of the tissues by all means in our power, for if we succeed in keeping the patient alive for some time and get rid of the œdema by appropriate treatment, it is reasonable to expect that the condition will change, and the tendency to œdema, with its immediate danger to life, will in many cases disappear. As in certain cases of acute nephritis, the withholding of salt may be of advantage, but unfortunately it too often happens that this treatment produces little or no effect.

Chronic Interstitial Nephritis, or Azotæmic Type.

There does not seem to be any theoretical objection to patients with hydræmic or azotæmic nephritis taking a fairly large amount of protein provided there is no retention of nitrogenous products in the blood. Indeed, some observers make use of blood urea or non-protein nitrogen estimations as a criterion to indicate whether or not the patient should receive a protein diet. They argue that no harm can arise from a protein diet provided there is no evidence of retention of nitrogen in the blood. On broad lines this is probably quite a useful method, but it

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must not be forgotten that the amount of nitrogenous waste products in the blood is entirely dependent on the nature of the diet. It might therefore happen that a patient who had already been taking a low protein diet would show no increase whatever in blood urea or other metabolic product, and yet this patient might be suffering from very advanced nephritis. Any decision, therefore, as to protein diet based on blood examination must be carefully considered in relation to the protein intake of the patient immediately before examination. In interstitial cases where nitrogenous retention is well marked it is generally considered that protein, especially in the form of meat, is on the whole contra-indicated. There is, however, no proof whatever that protein acts detrimentally even in advanced interstitial nephritis, but the clinical evidence suggests that it is best to limit the intake of protein in patients showing marked retention of nitrogen in the blood. This appears to be the general practice; and it is, no doubt, a good one. On the other hand, it seems quite certain that milder cases of interstitial nephritis are not benefited by very strict dietetic limitations. It is customary for many medical men to order a very strict regime, very low in protein content, in many cases in which the renal condition is by no means bad. In this country at present large numbers of men who contracted nephritis on military service, and who still show some albuminuria, are really suffering far more from the effect of unnecessarily restricted diet than from their renal disease. In the course of the last few years I have seen a large number of such cases in connection with the nephritis work carried out for the Ministry of Pensions. As the result of very many observations, I am convinced that in general patients suffering from interstitial nephritis of moderate severity should be allowed a fairly liberal diet, in which protein need not necessarily be cut down to any great extent. In very severe cases it is probably best to depend chiefly on carbohydrate food. The whole question of the effect of protein diet in kidney disease still

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requires much investigation, but it is certain that the custom of feeding patients practically on slops for long periods does much more harm than good. Badly fed patients suffering from interstitial disease are very likely to show marked anæmia and to develop a certain amount of œdema, especially in the lower extremities. The treatment of such cases by means of a good, though not excessive, protein diet, sometimes combined with a daily dose or two of urea, often works wonders. In fact, urea will sometimes succeed in keeping such patients more or less free from œdema when no other drug appears to have the slightest influence. When using urea in interstitial cases it is, of course, important to determine the blood urea, for no result is to be gained by giving urea to patients whose blood already contains large amounts of this material. That it can result in harm even in such cases is very improbable.

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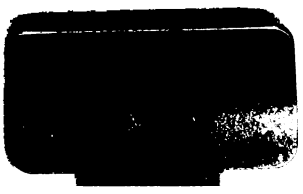

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